IMMEDIATE TREATMENT OF CEREBRAL INFARCTION

SEVEN YEARS' PERSONAL EXPERIENCE

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RECENT years have seen a revival of interest in the treatment of cerebral infarction, and some increase in knowledge of its ætiology, pathology, and mechanics. Formerly treatment had three main objects—preservation of life, prevention of nursing disasters, and rehabilitation of the disabled patient. No real attempt to influence the occlusion or its effect on the brain was made until Leriche and Fontaine (1934) suggested that stellate-ganglion block might improve the blood-supply of the infarcted brain and lessen the hemiplegia, even in longstanding cases. Since then this and other methods, which may involve the use of powerful and dangerous drugs, have been widely studied and employed; but the position is still far from clear, and medical opinion is sharply divided on the dangers and results of treatment.

In view of this it was decided to study all patients below the age of 80 with cerebral infarction admitted to Ashford Hospital in the 7-year period from January, 1952, to December, 1958. Owing to the generosity of my colleagues this has been a personal series, and some of these cases have already been reported (Carter 1957, 1959).

Definition and Ætiology

Cerebral infarction is here defined as an ischæmic condition of the brain, producing a persistent focal neurological deficit in the distribution of one of the major cerebral arteries. Consciousness may or may not be lost; there may be an obvious embolic source; and there should be no evidence of cerebral contusion, abscess, or hæmatoma. The cerebrospinal fluid (C.S.F.) is almost always normal to the naked eye.

For many years this condition was attributed to cerebral embolism or to cerebral thrombosis, depending on the speed of onset of symptoms and the presence or absence of an embolic source. But even this diagnosis was inferential, and what seemed a classical embolism could not always be substantiated as such at necropsy. It now appears that other conditions may produce cerebral infarction.

First, in many patients it has been impossible to demonstrate any clot either on arteriography (Livingston et al. 1955) or at necropsy (Hicks and Warren 1951), though later work suggests that some small proven thrombotic lesions escape arteriographic diagnosis (Alajouanine 1957), and that at necropsy small clots are often destroyed if the brain is cut while soft (Adams 1958). Therefore to say that clotting has not occurred because no clot has been found is probably unjustifiable.

Second, considerable attention has been focused on the internal-carotid and vertebral arteries in the neck, and the effects of arterial occlusion have been extensively studied (see Symonds [1957] and Hutchinson and Yates [1957]). There seems no doubt that arterial occlusion in the neck may produce cerebral infarction without a cerebral clot.

Third, cerebral arteriosclerosis has been shown to produce a state of general cerebrovascular insufficiency which may proceed to selective ischæmia or infarction by reason of focal arterial narrowing combined with systemic hypotension (Hausman 1958). Meyer and Denny-Brown (1957) showed that in monkeys collateral circulation of the brain is at first opened up by lowering of intraluminal pressure, but when the pressure falls below the critical level of 50 mm. Hg the whole system collapses and a reversible ischæmic cerebral anoxia is converted without thrombosis or embolism to irreversible infarction. But Adams (1958) regards this as an uncommon cause of major cerebral infarction, often accepted too easily at necropsy. He suggests that, if the arterial tree from aorta to the site of infarction is examined carefully, and if search is made assiduously for sources of embolism, some evidence of thrombotic occlusion of the vessel supplying the infarct will be found in the vast majority of cases.

The Series

One thousand and two patients below the age of 80 were admitted to Ashford Hospital with the clinical diagnosis of "stroke" between 1952 and 1958 inclusive (table I). Of these, five hundred and ten, who were thought to have cerebral infarction, form the subject of the present inquiry. The figures seem very consistent from year to year, and show that cerebral infarction accounted for just over half and cerebral embolism for less than a tenth of all "strokes".

TABLE I—CASES OF "STROKE" ADMITTED TO ASHFORD HOSPITAL, SHOWING SEX AND ÆTIOLOGY

Year	No. of cases	Sex		Ætiology		
		Males	Females	Embolism	Thrombosis	Hæmorrhage
1952	140	70	70	16	54	70
1953	154	75	79	18	62	74
1954	134	59	75	15	47	72
1955	140	65	75	9	61	70
1956	140	67	73	9	63	68
1957	147	70	77	10	66	71
1958	147	72	75	8	72	67
Total	1002	478	524	85	425	492

American figures (Murphy 1954) suggest that thrombosis accounts for 65%, embolism for 5%, and hæmorrhage (including subarachnoid hæmorrhage) for 30% of all strokes. Glynn's figures (1956) accord more closely with mine. Reviewing the consecutive cases of cerebrovascular disease admitted to a London general hospital during 4 years, he found that 56% had cerebral thrombosis, 36% had hæmorrhage, 3% had embolism, and 5% were undiagnosed.

Distribution and Type of Infarction

In the eighty-five cases of cerebral embolism the diagnosis was made on the very sudden appearance (often within seconds) of hemiplegia, hemianopia, or aphasia in the presence of auricular fibrillation, subacute bacterial endocarditis, recent coronary thrombosis, or mitral stenosis with sinus rhythm.

Such patients may, of course, have other cerebral disorders producing neurological deficit; but when a very sudden unilateral cerebral lesion develops during the waking hours

TABLE II—CASES OF CEREBRAL EMBOLISM

Year	No. of cases	Sex		Average age (yr.)	Hemiplegia		
		Males	Females		Right	Left	None
1952	16	5	11	52	5	10	1
1953	18	7	11	50	6	10	2
1954	15	5	10	48	5	8	2
1955	9	4	5	53	4	5	..
1956	9	4	5	56	4	4	1
1957	10	4	6	57	5	4	1
1958	8	3	5	55	3	4	1
Total	85	32	53	53	32	45	8

TABLE III—ÆTIOLOGY OF CEREBRAL EMBOLISM

Year	No. of cases	Ætiology					
		Mitral stenosis + fibrillation	Mitral stenosis	Fibrillation	Cardiac infarct	Subacute bacterial endocarditis	Thyrotoxicosis + fibrillation
1952	16	8	1	2	2	2	1
1953	18	10	2	2	2	1	1
1954	15	7	1	2	4	0	1
1955	9	4	1	0	3	0	1
1956	9	5	0	0	4	0	0
1957	10	3	0	0	6	1	0
1958	8	2	0	1	5	0	0
Total	85	39	5	7	26	4	4

in a patient with a known source of potential emboli, the diagnosis of cerebral embolism seems reasonable. A lumbar puncture was done in every case in an attempt to exclude a hæmorrhagic lesion.

All the cases of cerebral embolism are analysed in table II, which shows that since 1954 the incidence has decreased. Table III shows that the ætiology has changed also, with cardiac infarction tending to replace mitral stenosis as the commonest underlying heart lesion. The distribution of infarction in the eighty-five patients with cerebral embolism was mid-cerebral in seventy-seven (thirty-two with right hemiplegia, and forty-five with left hemiplegia), posterior-cerebral in four, anterior-cerebral in one, and vertebral-basilar in three.

In the four hundred and twenty-five patients with cerebral infarction not obviously due to embolism the diagnosis was based on a persistent focal neurological disorder in the distribution of one of the major cerebral arteries, in the absence of a history of head injury, and with C.S.F. normal to the naked eye. In addition there was no clinical evidence of tumour, abscess, or hæmorrhage.

A differential diagnosis between cerebral thrombosis, carotid or vertebral stenosis or thrombosis, and cerebral ischæmia with atheroma but without thrombosis is often impossible clinically, because carotid occlusion may equally produce either no disability at all, or attacks of transient cerebral ischæmia before infarction, or a classical complete "mid-cerebral type" infarction without warning. Similarly the infarction due to tissue anoxia associated with narrowed vessels often cannot be distinguished clinically from that due to thrombotic occlusion.

To obtain some idea of the relative frequency of the three main types of cerebral infarction either arteriography during life or necropsy is necessary. In this series I thought that routine carotid arteriography was unjustifiable, in view of its possible dangers, and particularly the general cerebral vasoconstriction often produced after puncture of the carotid and injection of the dye. However, when there was doubt about the diagnosis either on admission or during the course of the illness, arteriography was performed: the condition of two of the forty-five patients subjected to this investigation became worse. Of these doubtful cases twenty-seven were found to have carotid occlusion, but many more of the whole series must have had stenosis or occlusion of the carotid or vertebral arteries.

Occasionally the diagnosis was made on the history of ipsilateral recurrent visual loss with attacks of contralateral weakness affecting the arm mostly, or on the finding of a systolic murmur over the carotid opposite the C6 vertebra. The pulse over the affected carotid was rarely diminished. In fifty-two cases (from 1954 to 1958) a full postmortem examination of the cervical vessels was made in addition to the usual brain examination; twenty-two showed infarction with atheroma and without thrombosis, twenty had thrombus in the vessel supplying the infarcted area, and ten had cervical-carotid occlusion (complete in seven, and incomplete in three). If morbidity is proportional to mortality it seems that carotid occlusion may account for 20% of cases of cerebral infarction.

The meaning of the terms used must be strictly defined and agreed. "Cerebral thrombosis" has become so much a part of current medical terminology that it should, perhaps, still be used for patients with cerebral infarction, though there may be no clot and the occluding lesion may not even be cerebral. "Cerebral infarction", another possible term, is correct, but has the disadvantage of including patients with cerebral embolism. The term "cerebral thromboembolism" is accepted in North America. "Non-embolic cerebral infarction" (Carter 1959) is clumsy and not always correct, because a cerebral thrombus may occasionally produce subsequent infarction by distal embolism. Thus it may be as well to retain "cerebral thrombosis" as the provisional descriptive term for cerebral infarction not obviously due to embolism, and to make a more accurate final diagnosis when the appropriate investigations are completed.

Describing the onset and course of cerebral infarction is equally difficult. For the gradual type the following terms are in current use: "slow-onset stroke", "ingravescent infarction", "ingravescent stroke", and "stroke-in-evolution" (Fisher 1958). The word "stroke" has caused much confusion because it is sometimes used for the neurological deficit, sometimes for the state of consciousness, and sometimes for the first symptoms of brain damage. Moreover it may include all types of lesion from a hypertensive cerebral crisis, through embolism and thrombosis, to any sort of intracranial hæmorrhage. Because of this confusion it would be wise to banish the word from medical terminology, as we have banished "heart attack". "Ingravescent cerebral infarction" could then be used, being defined as cerebral infarction in which the neurological deficit has not yet become absolute, and in which the onset of symptoms takes time to develop. The exact time is not of great importance therapeutically, though arbitrarily over 2 hours is considered slow, and under 2 hours sudden, because in most patients the time falls well to one side of this line (Carter 1959).

TABLE IV—CASES OF NON-EMBOLIC CEREBRAL INFARCTION (CEREBRAL THROMBOSIS) SHOWING AGE, SEX, AND TYPE OF OCCLUSION

Year	No. of cases	Sex		Average age (yr.)	Type of occlusion		
		Males	Females		Anterior-cerebral	Mid-cerebral	Vertebral-basilar
1952	54	24	30	62	0	51	3
1953	62	30	32	65	0	56	6
1954	47	23	24	64	1	40	6
1955	61	30	31	65	1	52	8
1956	63	30	33	67	0	53	10
1957	66	34	32	64	1	56	9
1958	72	34	38	66	0	62	10
Total	425	205	220	65	3	370	52

Cerebral infarction was commonly distributed in the territory of the mid-cerebral artery; of the four hundred and twenty-five infarctions three hundred and seventy were in this group. Of the other infarcts, forty were in the vertebral-basilar territory, seven patients had posterior-inferior-cerebellar-artery occlusions, five had posterior-cerebral occlusions, and three were anterior-cerebral (see table IV).

Differential Diagnosis

The most important differential diagnosis of cerebral infarction is from cerebral hæmatoma, especially when the question of anticoagulant therapy is considered.

Subdural hæmatoma is less difficult to differentiate than intracerebral hæmatoma as a history of injury or fall, or fluctuation of signs—often with pupillary changes—may be helpful. Some loss of consciousness is common, and the neurological deficit spreads smoothly rather than irregularly, showing greater fluctuation than arises with infarction. Six patients of the present series were proved by carotid arteriography to have subdural hæmatoma, and three to have intracerebral hæmatoma.

TABLE V—RESULTS OF TREATMENT IN CEREBRAL EMBOLISM (ONE CASE FROM 1957 AND ONE FROM 1958 ARE NOT INCLUDED)

Year	No. of cases	Recovered	Improved	Not improved	Died	Treatment
1952	16	4	1	2	9	Repeated stellate block
1953	18	4	2	3	9	No treatment
1954	15	8	3	0	4	Single stellate block and anticoagulants
1955	9	5	1	1	2	Anticoagulants
1956	9	4	2	1	2	
1957	9	4	2	1	2	
1958	7	3	1	2	1	

Difficulty arises more often with primary intracerebral hæmatoma. This condition is easy to recognise in about 60% of cases, because the patient has a sudden attack with loss of consciousness, and the C.S.F. is bloody or xanthochromic. Hypertension is commonly severe, and, if the patient improves, headache and vomiting are prominent. Improvement is followed by further decline, with signs of cerebral compression, which if unrelieved leads to death. In some patients, however, the history and course is much more like cerebral infarction, and then the clinical diagnosis becomes difficult (Elkington 1958, Kelly 1958). Anticoagulants are likely to be used for the type of infarction with a quiet ingravescent onset and little loss of consciousness, the course of which is characterised by a step-like pattern of motor or sensory loss, with sudden increase or spread of weakness to previously unaffected areas. Headache is not prominent, some recovery follows within a few days, and signs of cerebral compression are absent. The patient is usually normotensive, the C.S.F. is clear, and the neurological deficit is in the distribution of one of the major cerebral arteries. Unfortunately some of these features have been found in primary intracerebral hæmatomata. McKissock et al. (1959) have published their experiences with two hundred and forty-four consecutive cases of this condition, proved either at operation or necropsy. They found that in 11% the onset was gradual, in 20% the C.S.F. was clear, in 23% the blood-pressure was normal, and in 46% consciousness was preserved. They also found that the accuracy of arteriography in diagnosis was below 70%.

In the present series little difficulty was found in diagnosing cerebral embolism. In the case of non-embolic cerebral infarction (suitable for anticoagulant treatment) the diagnosis was accepted if all the criteria of slow onset, step-wise course, normal blood-pressure, clear C.S.F., involvement of the territory of one cerebral artery, and little loss of consciousness were present.

Treatment

From 1952 to 1955 an attempt was made to assess the value of different forms of treatment, and to balance any benefit against any adverse effects. These results, with details of treatment, have already been recorded in full (Carter 1957, 1959).

Briefly, cerebral embolism was considered separately from the other forms of cerebral infarction. In 1952 repeated stellate-ganglion block was used, and the results were compared with an untreated series of patients admitted in 1953. In 1954 the patients were treated by a single stellate block followed by anticoagulant therapy, and the 1955 groups by anticoagulants alone. The results (table V) showed that the patients treated by stellate block did not improve, but those treated within a week of onset by anticoagulants with or without one stellate-ganglion block showed significant improvement.

The other forms of cerebral infarction were grouped together as " cerebral thrombosis ". In these patients similar methods were used, though the timing was different. In 1952 no specific treatment was given, but in 1953 repeated stellate block was used. In 1954 the inhalation of 5% carbon dioxide in oxygen through a B.L.B. mask was employed for 5 minutes every hour during the first 48 hours, as this is said to produce the greatest cerebral vasodilatation with increased blood-flow (Kety and Schmidt 1948). In 1955 all patients were treated by anticoagulants in the form of heparin by injection combined with oral phenindione (' Dindevan '). The results (table VI) showed that repeated stellate block produced no improvement, that carbon dioxide produced slight improvement, and that anticoagulants produced still more improvement. This became significant ($P < 0.05$) when the cerebral infarction was of slow onset and incomplete.

TABLE VI—RESULTS IN CEREBRAL THROMBOSIS: CASES UNSELECTED

Year	No. of cases	Recovered	Improved	Not improved	Died	Treatment
1952	54	13	12	9	20	No treatment
1953	62	14	16	8	24	Stellate block
1954	47	15	12	4	16	CO_2 inhalation
1955	61	20	16	9	16	Anticoagulants

After this experience, certain modifications were instituted during 1956–58. Stellate-ganglion block and carbon-dioxide therapy had not been of value in the treatment of cerebral infarction, and with two exceptions (cerebral embolism, and particularly ingravescent cerebral thrombosis if the paralysis was not complete) this was also true of anticoagulants.

The modifications that seemed necessary were three.

1. The age-limit of 80 was lowered to 70 (though occasional exceptions in the case of " young " septuagenarians were allowed) because visceral bleeding was more common in old people even with prothrombin-times only twice normal, and because of the greater difficulty in prothrombin-time control in this age-group.

2. The dose of anticoagulants was reduced. In the previous years, when full doses were given to raise the prothrombin-time to four times normal, bleeding often occurred in the patients over 60, but a smaller dose seemed to produce equally good results. The following method was used for all patients: (a) on admission heparin 12,500 units was given intravenously with phenindione 200 mg. orally; (b) two similar doses of heparin were given intramuscularly 6 and 12 hours after admission; and (c) during the second 24 hours phenindione 150 mg. was given in divided doses, and thereafter sufficient to keep the prothrombin-time between two and three times normal.

3. The third modification was to prolong the treatment from 2 to 4 weeks. Originally 2 weeks' treatment was considered adequate, as in thromboembolism of the limb vessels, but an occasional return of symptoms in the 3rd week suggested that this was not long enough for cerebral infarction. Therefore a full 3-week course was given, followed by a 4th week of gradually reduced dosage so that the prothrombin-time did not fall too quickly.

The results during 1952–55 had provided some indications for the treatment of cerebral infarction. Anti-

TABLE VII—CEREBRAL THROMBOSIS: RESULTS OF TREATMENT IN SELECTED INGRAVESCENT CASES

Year	Total no. of cases	Anticoagulant treatment					No anticoagulant treatment				
		No. of cases	Recovery	Improvement	No improvement	Death	No. of cases	Recovery	Improvement	No improvement	Death
1956	24	12	6	3	2	1	12	4	2	3	3
1957	20	10	5	3	1	1	10	4	2	2	2
1958	22	11	6	2	2	1	11	4	2	3	2
Total	66	33	17	8	5	3	33	12	6	8	7

TABLE VIII—RESULTS OF CONTROLLED TRIAL IN CEREBRAL THROMBOSIS OF SLOW ONSET, SHOWING IMPROVEMENT WITH TREATMENT IF LESION IS INCOMPLETE

Year	No. of cases	Anticoagulants				No anticoagulants			
		Lesion incomplete		Lesion complete		Lesion incomplete		Lesion complete	
		Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died	Recovered or improved	Unimproved or died
1956	24	6	2	3	1	4	3	2	3
1957	20	5	1	3	1	2	2	3	3
1958	22	5	1	3	2	3	4	3	1
Total	66	16	4	9	4	9	9	8	7

coagulants were most useful in cerebral embolism, and less so in certain types of cerebral thrombosis. Early treatment was reviewed and modified. During 1956–58 all patients with cerebral embolism were treated with anticoagulants unless there was blood in the C.S.F., unless they were over 70, and unless their diastolic blood-pressure was over 120 mm. Hg. Only two patients were rejected on these grounds, and twenty-five admitted in these 3 years were treated with anticoagulants. The results, shown with the previous years' results in table V, are consistent.

The situation was different with cerebral thrombosis because the indications for treatment were not so clear, and the contraindications were more obvious than in overt cerebral embolism. Hence selection of patients for treatment during 1956–58 seemed desirable. Patients with a history of onset of lesion developing within 48 hours and lasting more than 2 hours, with a diastolic pressure below 120, and with no macroscopic evidence of blood in the C.S.F. were selected for study. During these 3 years two hundred and one patients were admitted with the diagnosis of cerebral infarction, without obvious embolic source, and in sixty-six of these the onset was slow, as defined above. They were divided into two equal groups, and alternate patients were treated with anticoagulants. The results are shown in table VII.

Results

Assessment

With few exceptions most of the neurological recovery from cerebral infarction takes place in the first 4 weeks, and very little change, apart from that due to re-education and adaptation, can be expected after 3 months. Certain workers—notably Leriche and Fontaine (1934) in France—have held more optimistic views, but experience in this country is less encouraging. The final assessment was made by examination 6 months after infarction, and the patients were simply divided into four groups: recovered, improved, not improved, or died.

" Recovered " meant that the patients noticed little or no disability and were able to resume successfully their former occupation. Some loss of fine-movement dexterity was considered compatible with recovery if the above criteria were fulfilled. Probably all patients with initial hemiplegia continue to show slight permanent pyramidal signs. " Improved " meant that some useful movement was possible at elbow and wrist, and that the patient could get about with slight assistance. " Not improved " indicated no return of arm movement below the shoulder, though some leg function was regained. Almost all patients who survive infarction with hemiplegia regain some movement of the shoulder and the leg.

Analysis of Results

The results in patients with cerebral embolism are recorded in table V. In 1952–53 the results were good (" recovered " or " improved ") in eleven out of thirty-four patients, and this 33% recovery was unchanged by stellate-ganglion block. This compares with the usual recovery-rate of about 40% (Wells 1959). In the following years forty-nine patients were treated with anticoagulants (preceded in 1954 by a single stellate block) and in thirty-three the results were good, representing 66%. These figures are significant ($P=0.025$), and the proportion of patients who recovered was doubled in the treated group.

The results in patients with cerebral thrombosis were rather harder to assess (table VI). The natural history suggests that just about half the patients recover, about a third die within a year, and the remaining sixth are unimproved. With carbon-dioxide therapy a slight improvement in these figures was obtained, and with anticoagulant therapy further slight improvement occurred so that 60% showed fairly good recovery.

The usual prognostic factors, studied in all the groups, were equally distributed. It soon became apparent that old age, severe and extensive infarction, prolonged unconsciousness, delay in admission to hospital resulting in dehydration and bedsores, severe hypertension, and a history of previous strokes were all bad signs. The patient most likely to die was the neglected old man in poor condition with signs of longstanding ischæmic heart-disease. Lesions of slow onset carried an overall better prognosis than those of rapid onset, and this improvement could be bettered by anticoagulants, particularly if the lesion had not become complete by the time treatment was begun.

The results in the patients selected along the above lines during 1956–58 are shown in table VII. If the " recovered " and " improved " groups are taken together, as opposed to those who died or did not improve, it will be seen that twenty-five of the thirty-three patients who were treated did well as opposed to eighteen of the thirty-three who were untreated. This is 75% against 54%, and represents a just significant improvement ($P=0.05$).

If the patients are selected further according to the completeness or not of the lesion when treatment was begun (table VIII), greater improvement can be seen. The recovery-rate in the treated " incomplete " group was 80%, and in the treated " complete " group 69%. In the untreated incomplete group the recovery-rate was 50% and in the untreated complete group 53%. This improvement from 50 to 80% is significant ($P<0.05$), suggesting that the best results will be in the patient whose lesion is slowly getting worse.

Discussion

The results of this investigation suggest that the only specific treatment likely to help patients with cerebral infarction is anticoagulant treatment. This has been shown to be of some value for patients with recent cerebral embolism, or with infarction of slow onset, although further selection of patients is necessary in terms of hypertension, appearance of the C.S.F., and age. Experience has also shown that the indications have

become fewer and the criteria for treatment more stringent.

Mechanism of Treatment

The mechanism of anticoagulant treatment once cerebral infarction has taken place is not completely understood, but the benefit must arise in one or more of three ways. Spread or propagation of clot (which sometimes occurs both distally and centrally from the original thrombosis) may be prevented; and, since this spread often involves anastomotic vessels, anticoagulants may keep the infarcted area from enlarging. They may also prevent initial clot formation if the infarction were caused by atheromatous narrowing without thrombosis, combined with systemic hypotension, and they may prevent distal embolism in the case of thrombosis of large vessels. This seems to be particularly useful in infarction associated with carotid and vertebral stenosis (Symonds 1957). Indeed one is tempted to suppose that the stepwise progress of ingravescent cerebral infarction is produced by repeated distal embolism, thus accounting for the curious paradox in this report—namely, that the most acute infarct from cerebral embolism and the most chronic from ingravescent cerebral ischæmia are the only types helped by anticoagulants. If this is so then the comparative freedom from local hæmorrhage in this series may be put down to the fact that clinical embolism often affects healthy arteries, and distal embolism affects the smaller cerebral arteries which are known to escape atheroma. Conversely, in sudden lesions due to cerebral thrombosis the clot is presumably situated at the most unhealthy part of the vessel, and in this type of case anticoagulants have been ineffective and occasionally harmful. One must also recognise that apparently adequate prolongation of the prothrombin-time will not always prevent thrombosis, and all physicians experienced in this work have known the mortifying disappointment of seeing a major thrombus strike at this time.

Dangers of Treatment

The evident dangers of anticoagulant treatment, which have been rightly emphasised by most authors, are three in number. The first is bleeding into and around the infarcted brain; the second is major visceral bleeding producing hypotension; and the third is the risk of treating intracranial hæmatomata with anticoagulants because of errors of diagnosis.

Medical opinion is sharply divided on the possibility and extent of bleeding around or into infarcted brain. Experimental work suggests that anticoagulants do considerable harm in this way.

Sibley et al. (1957) showed that experimental hæmorrhagic cerebral infarcts in dogs would bleed further after the administration of dicoumarol, but when the infarcts were anæmic no such tendency was found. Moyes et al. (1957) showed that infarctions produced in dogs by injecting plastic vinyl acetate into the internal carotid artery were more hæmorrhagic in animals having anticoagulants. Similarly Peterman et al. (1959) produced cerebral infarction in dogs by the intracarotid injection of blood-clot. After 3 days about half the animals were given dicoumarol, and at the end of 15 days the infarctions in the treated animals were conspicuously more hæmorrhagic and the mortality was higher.

Clinically, however, the evidence against anticoagulants is less strong. Fisher (1958) found no evidence that anticoagulants cause hæmorrhage into infarcted brain, and my experience (Carter 1957, 1959) agrees with this.

Similarly Wright and McDevitt (1954) found no clinical evidence that anticoagulant treatment was harmful, even in hæmorrhagic cerebral infarction. Brain (1957) thinks it unwise to give anticoagulants within at least 3 weeks of an attack of cerebral infarction, and this view is supported on the Continent by de Morsier and Tissot (1957). Vastola and Frugh (1959) have reported a very disturbing series of fifty-five consecutive patients with recent cerebral infarction treated by anticoagulants. There was no control series, but the authors did not think their patients showed improvement as compared with that " expected in a similar group ". Twenty of the fifty-five patients bled in various parts of the body, and in four anticoagulants were blamed for extensive brain hæmorrhage—three into the infarct and one elsewhere. On the other hand Wells (1959) treated with anticoagulants twenty-nine patients with 34 attacks of cerebral embolism, with results better than in his untreated series and without intracranial bleeding.

Two examples will show the danger of attributing cerebral hæmorrhage to anticoagulant therapy in patients who are being treated for cerebral infarction.

CASE 1.—A man, aged 67, was admitted in November, 1958, with 3 weeks' history of progressive vertigo, left homonymous hemianopia, and weakness of the legs. He had had a transient right hemiparesis 12 months previously, with some personality deterioration. On the day of admission he was found lying on the floor, dazed and stuporose, with left hemiparesis. Lumbar puncture showed clear C.S.F. under normal pressure, containing 9 lymphocytes per c.mm. and 50 mg. of protein per 100 ml. Next day the left hemiparesis was deeper and bilateral facial weakness had appeared. Basilar stenosis with possible thrombosis was diagnosed and anticoagulant treatment was begun. All the signs improved except the hemianopia, which remained complete.

After discharge the patient was advised to continue anticoagulants (phenindione 50 mg. daily), which kept his prothrombin-time steady at about 30 seconds. 6 weeks later he complained of violent headache, became rapidly unconscious, and died (the prothrombin-time was then 20 seconds). At necropsy a massive subarachnoid hæmorrhage was found, and anticoagulants were blamed until it was seen that a friable tumour, adherent to the right wing of the sphenoid, had ruptured the cavernous sinus. Sections showed that this was a hitherto unsuspected cellular meningioma. Basilar stenosis was present, the right posterior-cerebral artery was grossly narrowed, and the right occipital lobe showed recent softening; neither the cerebral nor cervical arteries contained thrombus.

CASE 2.—A man, aged 68, was admitted in March, 1959, with an increasing left hemiparesis of 6 hours' duration. The left arm was completely paralysed, but weakness of the left leg was moderate. He had no sensory loss or hemianopia. His blood-pressure was 180/115, and the C.S.F. was clear. Anticoagulant therapy was begun. His hemiparesis improved, and he was discharged 4 weeks later, using a stick and with movement of all joints in the left arm. A month later, when he was readmitted with a return of left-sided weakness, it was decided to use long-term anticoagulant therapy, and he was stabilised on phenindione 75 mg. daily. 4 months later he was again admitted, now moribund, and with signs of cerebral hæmorrhage. This diagnosis was confirmed at necropsy, a large hæmorrhage having destroyed the right cerebral hemisphere. The prothrombin-time of 12 seconds on the day the patient died was disbelieved, until his relatives explained that he had not taken his tablets for at least a month before his death.

The second danger of treatment—that of visceral bleeding—seemed at first a major risk, particularly in the elderly. In the second half of this series, when the dosage of anticoagulants was reduced, 17 minor hæmorrhagic episodes arose in nine patients. Of these hæmaturia accounted for 7, epistaxis for 5, subconjuctival hæmorrhage for 3, and facial bleeding after shaving for the other 2. In only one patient was the prothrombin-time found to be over 40 seconds, and in all the patients treatment was resumed after a 2-day interval. Luckily no major visceral bleeding was encountered in the last 3 years

and no patient had to be withdrawn from the treated group. Some people may bleed severely, of course, even if the prothrombin-time is not unduly raised, and the patient's condition is a more important guide than the results of blood estimations. Thus the continued use of anticoagulants is always dangerous if any visceral or serious superficial bleeding arises, even though the prothrombin-time is reasonably low.

The third danger is mistaken diagnosis. The differentiation between cerebral infarction and intracranial hæmatomata has already been discussed. Fortunately the type of infarction that can suitably be treated by anticoagulants is not the most likely to be mistaken for hæmorrhage, although a small but disturbing proportion of intracerebral hæmatomata have a slow onset without loss of consciousness, without hypertension, and with clear C.S.F. (McKissock et al. 1959), all of which are usually characteristic of infarction. But in addition the stepwise course of ingravescent infarction, and its adherence to the distribution of a major cerebral artery, are helpful in avoiding obvious error.

Indications for Treatment

Selection of patients for treatment with anticoagulants depends largely on the interpretation of the results in this series. In the first 4 years under review comparison with an untreated series suggested that vasodilators, including stellate-ganglion block, made no difference to the natural history of cerebral infarction. Short-term anticoagulant therapy improved the prognosis of cerebral embolism significantly, but not that of cerebral thrombosis, unless the patients were selected carefully. Significant improvement was obtained only if the infarction was of slow onset and the neurological deficit not apparently complete.

During the second part of the investigation the anticoagulant treatment was modified, and, in view of previous difficulties, the criteria for selecting patients were better. To test the validity of the previous years' impression, alternate patients were treated in the cerebral-thrombosis group of slow onset. The treated group improved significantly ($P=0.05$), and this became more significant ($P<0.05$) if the lesion was incomplete when treatment was begun. Anticoagulant treatment seems, therefore, to be indicated in all patients with cerebral embolism and in all patients with progression of cerebral infarction of over 2 hours' duration, particularly if the disability at the time of treatment is not complete. These criteria for selection of patients are subject to the overriding contraindications discussed below.

Contraindications to Treatment

Past history.—If the patient had had previous hæmatemesis or melæna, prolonged dyspepsia or proved peptic ulceration or if the control prothrombin-time was raised on admission, suggesting hepatic disease, then anticoagulants were thought to be contraindicated.

Age—During the first 4 years of this review the age-limit for treatment was 80. In the over-70 group difficulty was experienced from time to time in controlling prothrombin-time, and superficial hæmorrhage, hæmaturia, and epistaxis were more frequent and more severe. One patient died of uræmia from hæmorrhage into the renal pelves, and another bled per rectum producing hypotension and an extension of the infarction. It was decided, therefore, that with few exceptions 70 was probably the upper limit for treatment. An arbitrary rule is obviously impossible, and after further experience this limit may be raised.

Hypertension.—Severe hypertension undoubtedly favoured a hæmorrhagic infarct or even intracerebral hæmatoma, particularly if the fundi showed hæmorrhages, papillœdema, or exudates. Renal hypertension and evidence of renal failure also seemed to promote easy bleeding. We decided arbitrarily that a diastolic blood-pressure of 120 mm. Hg should be the upper limit for anticoagulant therapy, and afterwards complications of therapy were less.

C.S.F.—Any blood or xanthochromia in the C.S.F. was regarded as an absolute bar to anticoagulant treatment, but lymphocytosis and increased protein-content (found in about half the patients) were not thought to be contraindications. Because a hæmorrhagic peripheral infarction which starts slowly will occasionally produce blood in the C.S.F., some cases of ingravescent cerebral infarction will consequently not be treated with anticoagulants. It seems reasonable, however, to suppose that the dangers of increased bleeding in this type of case outweigh any possible advantages.

Sudden onset was considered a contraindication because in the first 4 years anticoagulant treatment did not improve the natural history of this type of case. No doubt some of the patients found unconscious in their beds had ingravescent infarction; but the danger of a concealed intracerebral hæmatoma seemed too great, and they were excluded from treatment.

Unconsciousness.—In patients with cerebral embolism unconsciousness was not regarded as a contraindication to anticoagulant treatment. In the cases admitted unconscious with a lesion of slow onset it seemed unwise to give anticoagulants at once because of the possibility of cerebral hæmorrhage. If, however, consciousness was regained fairly rapidly, and then the neurological deficit began to increase, anticoagulants were thought safe unless there were other contraindications.

Conclusions

The above indications and contraindications, together with the results of this survey, suggest that anticoagulants play, on the whole, a small part in the immediate treatment of cerebral infarction. But in a select group of patients their part is important. These patients comprise those with cerebral embolism and those who remain conscious or regain consciousness quickly after the onset of cerebral thrombosis when paralysis is incomplete and worsening.

Summary

A series of five hundred and ten consecutive patients with cerebral infarction, admitted to Ashford Hospital, Middlesex, from the beginning of 1952 to the end of 1958, was studied personally.

Extracerebral vascular insufficiency was not uncommonly the cause of intracerebral infarction. In differential diagnosis it was sometimes difficult to separate cerebral infarction from intracerebral hæmatoma.

During the first 4 years of this study different methods of treatment were investigated. Vasodilator drugs and stellate-ganglion block failed to influence the natural course of cerebral infarction.

During the second half of the study anticoagulant drugs were beneficial in the immediate treatment of cerebral embolism, the follow-up period being 6 months.

Sudden and complete non-embolic cerebral infarction, particularly when accompanied by unconsciousness, was not improved by any specific treatment.

During the last 3 years of this study a controlled clinical trial was undertaken to decide whether anticoagulants would help the patient with ingravescent infarction (over 2 hours) or signs of increasing paralysis. The best results were in patients who were conscious and whose lesion was incomplete when treatment was begun.

It is a pleasure to thank my colleagues, Dr. K. D. Keele and Dr. J. E. Royds, for allowing me access to their patients, and for their valuable suggestions regarding this article.

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CLINICAL COURSE OF UNCOMPLICATED ACUTE TUBULAR NECROSIS

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ACUTE oliguric renal failure is present when the volume of urine produced by the kidneys is insufficient for maintenance of the normal body internal environment. In chronic renal failure the clinical and biochemical status of the patient may change little for long periods, sometimes for several months or even years. By contrast, in acute renal failure there is progressive and continuous deterioration unless diuresis occurs or some form of dialysis is applied.

The natural history of cases of acute oliguric renal failure is extremely varied because the condition may be caused by many unrelated types of disease; for example, there may be lesions of the major or minor renal arteries or veins, glomerular lesions of acute glomerulonephritis or polyarteritis nodosa, proximal tubular necrosis due to nephrotoxic drugs or poisons, ischæmic tubular lesions including acute tubular necrosis, renal cortical necrosis, acute papillary necrosis, or an acute exacerbation of chronic renal disease or bilateral ureteric obstruction.

The commonest cause of acute oliguric renal failure is acute tubular necrosis; and this is singularly important because, if the patient survives, recovery is accompanied by full restitution of renal function. Uncomplicated acute tubular necrosis is usually a disease of predictable course, and, if properly treated, is relatively benign. When the condition is complicated by infection or by associated injuries, whether accidental or surgical, it is much less predictable and much more serious. Teschan et al (1955) emphasised this difference as a result of their experience of acute tubular necrosis in the injured and wounded in the Korean campaign. The course of the disease in their patients, particularly those with severe injuries to voluntary muscle, proved to be much more fulminant than in the average civilian patient without such complications. A similar difference is apparent in the series of civilian cases reported recently by Parsons and McCracken (1959) and by Bluemle et al. (1959). The proportion of fatal cases was less than 25% in patients in whom the acute tubular necrosis was due to medical or obstetric causes, but more than 70% when it was complicated by trauma. Biochemical deterioration is more rapid in the surgical group. There is frequently a dramatic rise of plasma-potassium, uncontrolled by enteral cation-exchange resins, and there is a rapid fall of plasma-bicarbonate due to uræmic acidosis. In a series of 220 cases of acute oliguric renal failure of all types referred to Hammersmith Hospital for dialysis by an artificial kidney, the prognosis has been good where acute tubular necrosis was due to a medical or obstetric cause. In contrast, the prognosis has been much worse in those patients in whom acute tubular necrosis was secondary to severe injuries or surgical operations. A high proportion of such patients

TABLE I—RECOVERED CASES OF ACUTE TUBULAR NECROSIS

Case no.	Age (yr.)	Sex	Diagnosis	Duration of oliguric phase (days)	Hæmo-dialysis
1	28	F	Induced abortion at 20 weeks	13	−
2	37	F	Induced septic abortion at 12 weeks	15	−
3	19	F	Induced septic abortion at 18 weeks	10	+
4	29	F	Induced septic abortion at 14 weeks	20	++
5	23	F	Induced septic abortion at 16 weeks	14	+
6	29	F	Induced septic abortion at 20 weeks	13	+
7	31	F	Induced abortion at 13 weeks	12	−
8	24	F	Induced septic abortion at 12 weeks	22	+
9	19	F	Spontaneous abortion at 19 weeks	9	−
10	26	F	Abortion at 24 weeks (hydatidiform mole)	14	−
11	32	F	Concealed accidental hæmorrhage at 30 weeks	4	−
12	30	F	Accidental hæmorrhage at 36 weeks	10	−
13	20	F	Infective hepatitis with premature delivery at 36 weeks	12	+
14	31	F	Accidental hæmorrhage at 34 weeks	12	+
15	35	F	Postpartum hæmorrhage	13	−
16	24	F	Postpartum eclampsia	8	+
17	20	M	Carbon-tetrachloride poisoning (by inhalation)	11	+
18	26	M	Carbon-tetrachloride poisoning (by ingestion)	13	−
19	36	M	Carbon-tetrachloride poisoning (by inhalation)	7	−
20	27	M	Mercuric cyanide poisoning (by ingestion)	12	−
21	33	M	Arsine-gas poisoning with hæmolysis and oliguria	29	++
22	55	F	Staphylococcal pneumonia with scarlatiniform rash	10	+
23	29	F	Staphylococcal pneumonia	12	−
24	26	M	Influenza	14	+
25	34	M	Leptospirosis; *L. icterohæmorhagiæ*	6	+
26	23	M	Oliguria and jaundice of unknown cause	9	+
27	41	M	Oliguria and jaundice of unknown cause	14	−
28	62	M	Oliguria of uncertain cause	12	−

died of their injuries or from complicating infection despite carefully controlled conservative treatment and in many cases repeated hæmodialysis.

We describe here the natural history of uncomplicated acute tubular necrosis in a selected group of 28 patients in whom the primary cause of the disease was medical or obstetric (table I). All of these patients recovered completely with or without hæmodialysis. This selection avoids the difficulties due to the irregular and unpredictable course when the condition is complicated by uncontrolled infection or extensive tissue damage, and permits analysis of the full course of the disease from onset to full recovery. The series may be unrepresentative of all examples of uncomplicated acute tubular necrosis, since probably the more severe cases are referred to centres equipped for hæmodialysis. This difficulty of sampling is, however, almost universal in descriptions of disease based on the experience of a single hospital. 5 patients with proximal tubular necrosis have been included since their course seemed to be identical with that of acute tubular necrosis.

During this period deaths in cases diagnosed on admission as uncomplicated acute tubular necrosis numbered 11 (table II). 3 of these patients were proved at necropsy to have renal cortical necrosis with almost complete destruction of all nephrons. The fatal cases will be described after the analysis of the 28 patients who recovered.

Management

All patients were treated by a standard conservative regime. The diet consisted of a 20% solution of lactose by mouth, a volume of X+400 ml. daily being given from November to April, and X+500 ml. daily from May to October, where X ml. is the total volume of the measurable fluid loss from the patient on the previous day. When intractable uræmic vomiting occurred, the same volume of sterile 40% glucose was given by infusion, preferably into the superior vena cava, but at times into the inferior vena cava, instead of by mouth. Soluble insulin was given by injection when the blood-sugar was over 200 mg. per 100 ml. Sulphonamides or antibiotics were given only in cases with established infection, but all patients were isolated and standard methods of barrier nursing were used. Infusions of packed cells were given in amounts large enough to maintain the hæmoglobin concentration above 10·2 g. per litre (70% Haldane). Non-virilising androgens in the dosage recommended by McCracken and Parsons (1958) were given to the female patients during the latter half of the series. Blood-urea and plasma potassium and bicarbonate were measured daily, and electrocardiography was performed daily throughout the whole of the oliguric stage. Hæmodialysis was carried out by a rotating-drum artificial kidney when any one of the following indications was present: (*a*) blood-urea above 400 mg. per 100 ml.; (*b*) plasma-bicarbonate below 12 mEq. per litre; (*c*) plasma-potassium above 7·5 mEq. per litre, despite therapy with cation-exchange resins by mouth (Elkinton et al. 1950, Evans et al. 1953); (*d*) electrocardiographic evidence of intraventricular block with widening of the QRS complexes from hyperkalæmia; (*e*) uræmic stupor, coma, vomiting, hiccough, or fits.

Appropriate supplements of sodium and potassium salts were given in the diuretic stage, usually in amounts equal to the urinary losses of the previous day. A diet of carbohydrate alone was continued until the blood-urea fell below 100 mg. per 100 ml., unless the patient became extremely hungry and demanded solid food.

Stages

The course of the disease, as suggested by Bull et al. (1950), has been divided into an onset stage, oliguric stage, early diuretic stage, late diuretic stage, and convalescent stage; but the definitions of the five stages adopted here are more precise and better adapted for clinical use:

Onset stage.—This is the short period between the acute event causing the renal damage and the development of

TABLE II—FATAL CASES OF ACUTE TUBULAR NECROSIS AND RENAL CORTICAL NECROSIS

Diagnosis and case no.	Age (yr.)	Sex	Diagnosis	Stage of illness at death	Hæmo-dialysis	Postmortem findings
Acute tubular necrosis:						
1	38	F	Induced abortion at 24 weeks; terminal septicæmia	10th day diuretic phase	+	Multiple hæmorrhagic abscesses (lungs, kidneys, heart, and brain); renal tubular necrosis
2	37	F	Induced septic abortion at 12 weeks; pelvic cellulitis	13th day oliguric phase	−	Purulent pericardial effusion with myocardial abscess; pelvic peritonitis; renal tubular necrosis
3	29	F	Induced septic abortion at 16 weeks; pelvic peritonitis	10th day oliguric phase	+	Ruptured uterus with general peritonitis; renal tubular necrosis
4	23	F	Induced septic abortion at 18 weeks	6th day diuretic phase	+	Renal tubular necrosis; septicæmia with pyodermia
5	75	F	Sensitivity reaction to sulphonamides	14th day oliguric phase	+	Renal tubular necrosis; no evidence of glomerulitis
6	54	M	Overdose of morphine with hypotension; staphylococcal pneumonia	Late diuretic phase—blood-urea 100 mg. per 100 ml.	− −	Lung abscess with empyema; healed renal tubular necrosis
7	61	M	Pneumonia; hypotension	2nd day oliguric phase	−	Hæmorrhagic pulmonary œdema; no evidence of pneumonia; renal tubular necrosis
8	57	M	Acute tubular necrosis due to pancreatitis	17th day oliguric phase	++	Renal tubular necrosis; hæmorrhagic pancreatitis
Renal cortical necrosis:						
9	35	F	Concealed accidental hæmorrhage at 28 weeks; cerebral hæmorrhage	9th day oliguric phase	+	Symmetrical renal cortical necrosis; cerebral hæmorrhage
10	32	F	Concealed accidental hæmorrhage at 32 weeks; staphylococcal septicæmia	19th day early diuretic phase	+	Symmetrical cortical necrosis of kidneys
11	35	F	Concealed accidental hæmorrhage at 27 weeks; septicæmia	18th day oliguric phase	++	Symmetrical renal cortical necrosis

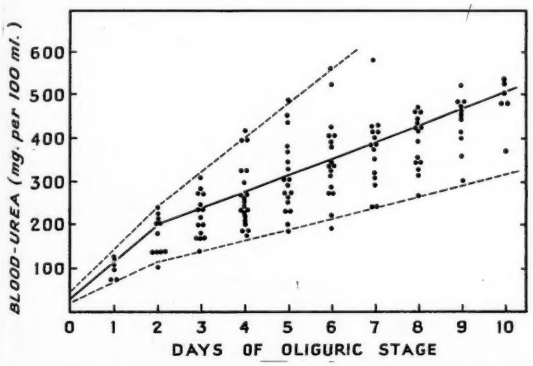

Fig. 1—The rise of blood-urea during the oliguric stage of acute tubular necrosis before hæmodialysis or in undialysed patients.
The rate of rise of blood-urea is greater in the first two days. The regression line is calculated from days 2 to 7 inclusive, as after day 7 many of the higher blood-urea values have been reduced by hæmodialysis.

established oliguria with a urine output in an adult patient of less than 400 ml. per day.

Oliguric stage.—This is the interval between the onset stage and the first day when the urine volume is consistently more than 400 ml. per day.

Early diuretic stage.—This is the period between the end of the oliguric stage and the first day when there is an unequivocal and sustained fall of the blood-urea.

Late diuretic stage.—This is the period between the end of the early diuretic stage and the first day on which the blood-urea is consistently lower than the upper limit of normal—i.e 45 mg. per 100 ml.

Convalescent stage.—This is the period in which, although the blood-urea is normal, the patient is still unable to engage in normal activities or duties.

In this account of the clinical course of uncomplicated acute tubular necrosis, the daily urine volume and the values of blood-urea are considered to be the two most important biochemical indices. Although concentrations of plasma potassium and bicarbonate are of especial value in assessing the need for hæmodialysis, they may both be influenced by relatively minor therapeutic procedures such as the administration of cation-exchange resins or infusions of sodium lactate. Their values do not necessarily therefore reflect the course of the disease. In contrast, the blood-urea will rise continuously unless spontaneous diuresis occurs or hæmodialysis is applied.

Onset Stage

Since all patients were referred from other hospitals early in the oliguric stage there was unfortunately no opportunity to study the patients in this important stage of the disease.

Oliguric Stage

Complete anuria is extremely rare in acute tubular necrosis. Urethral catheterisation was avoided in order to prevent infection, and it is therefore impossible to give the precise urinary volume produced during each day of the oliguric stage. The calculated mean daily volume during the first six days was 75 ml. and the mean of the whole oliguric stage was 150 ml., suggesting a slow increase of urinary volume during this stage of the disease.

The mean duration of the oliguric stage was 12·5 days (S.D. 5·0 days), which is similar to the mean duration reported by Bull et al. (1950) and Swann and Merrill (1953). The rate of rise of blood-urea was greater during the first two days of the oliguric stage than in the succeeding days (fig. 1), the mean blood-urea rising to 200 mg. per 100 ml. by the end of the second day. This probably reflects a temporary increase of catabolism with a greater production of urea by breakdown of tissue proteins due to the initial insult. In addition, the rate of loss of urea in the small amounts of urine produced and in sweat, vomit, and fæces is roughly proportional to the concentration of urea in the blood. After the second day, the rate of rise of blood-urea was reduced by treatment, and averaged 34 mg. per 100 ml. per day. In some patients the rate of rise of blood-urea was not greater than 25 mg. per 100 ml. per day, which represents the theoretical minimum assuming a low endogenous protein breakdown of 40 g. per day (Gamble 1951). In 3 patients the rate of rise of blood-urea was unusually great and hæmodialysis was required early in the oliguric stage. 1 patient had an acute hæmolysis due to arsine poisoning, another had severe staphylococcal pneumonia, whilst the 3rd had leptospirosis with considerable liver damage. In all 3 cases there was probably an increased rate of protein breakdown from the associated condition.

Of the 28 patients 13 were treated by hæmodialysis: 11 had a single treatment, and 2 were dialysed on two occasions. After the fifteen dialyses (twelve in the oliguric stage and three in the early diuretic stage) the subsequent daily rise of blood-urea continued unchanged (fig. 2). Hæmodialysis causes the biochemical changes to revert to those found earlier in the oliguric stage, and has no other influence on the course of the disease. The rate of rise of blood-urea on the first day after hæmodialysis is usually greater than on succeeding days (fig. 2). This probably reflects equilibration of the relative excess of urea in the intracellular compartment with that in the extracellular fluid and plasma. The artificial kidney clears urea first from the blood and extracellular fluid.

Early Diuretic Stage

Division of the diuretic stage into an early and late stage is of great clinical value because the amount of urea excreted during the early diuretic stage is approximately equal to that formed from endogenous protein breakdown, and there is usually no fall of the blood-urea. Indeed, during the early diuretic stage the clinical and biochemical

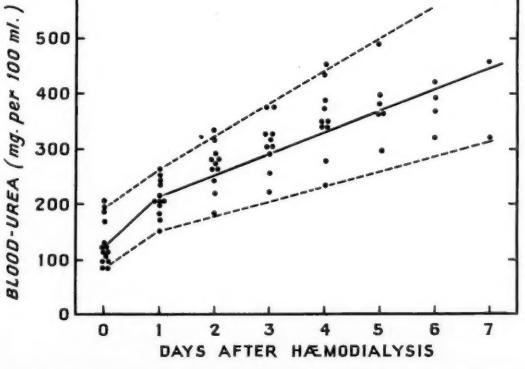

Fig. 2—The rise of blood-urea during the oliguric stage of acute tubular necrosis after hæmodialysis.
The rate of rise is greater on the first day after dialysis. Subsequently the mean rise is identical with that shown in fig. 1.

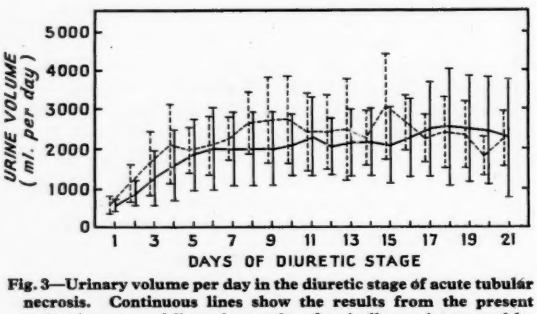

Fig. 3—Urinary volume per day in the diuretic stage of acute tubular necrosis. Continuous lines show the results from the present series, interrupted lines the results of a similar series treated by Bull et al. with a greater fluid intake during the oliguric stage, with mean and standard deviations in each case.

The mean volume in the series of Bull et al. is consistently greater until the 17th day of the diuretic stage.

status of the patient does not improve and frequently continues to deteriorate. In the late diuretic stage, however, when the blood-urea falls, there is steady and progressive improvement. Hæmodialysis may have to be carried out in the early diuretic stage, but is rarely, if ever, indicated in the late diuretic stage. As soon as the daily urinary volume consistently exceeds 400 ml. there is usually a steady daily increase at a mean rate of 280 ml. per day until a volume of about 2000 ml. per day is reached after five or six days (fig. 3). Thereafter the mean daily urinary volume is stabilised at 2000–2500 ml. The mean duration of the early diuretic stage was 4·7 days (S.D. 3·1), and stabilisation of the urinary volume roughly coincided with the day on which the blood-urea started to fall.

Late Diuretic Stage

Urine volumes in the late diuretic stage are now less than in cases treated ten to twelve years ago (Bull et al. 1950). It was then customary to give patients more fluid during the oliguric stage—usually 1000 ml. more than the total fluid loss on the previous day. In fig. 3 the mean urinary volumes in the present series are compared with those in a similar series of cases of acute tubular necrosis reported by Bull et al. (1950). The mean urinary volumes are consistently higher in the latter series until the seventeenth day of the diuretic stage ($\chi^2=95$; $P<0.001$). If it is assumed that the patients of Bull et al. received an excess fluid intake of 500 ml. each day during the twelve days of the oliguric stage, the average total excess given to each patient was 6 litres. Comparison of the urinary volumes in fig. 3 shows that the patients of Bull et al., on an average, each excreted 6·5 litres more urine than the patients of the present series during the first seventeen days of the diuretic stage. This suggests that the greater diuresis in the patients of the earlier series was largely due to the higher fluid intake during the oliguric stage. It has been claimed (Black 1957) that high urinary volumes in the diuretic stage of acute tubular necrosis are chiefly due to osmotic diuresis, the osmotic load per single functioning nephron being abnormally high. The observations recorded here suggest, however, that at least part of the diuresis in patients treated in the past was due to water diuresis from prior over-hydration. Whereas an individual with normal renal function would excrete an excess body-water content of 6 litres within twenty-four hours, a patient in the diuretic stage of acute tubular necrosis has gross impairment of renal function (Swann and Merrill 1953) and requires over two weeks to excrete excess water which could be eliminated by healthy kidneys within a single day. An excess body water content of 6 litres is equivalent to 13% of the normal total body-water and could cause considerable water intoxication.

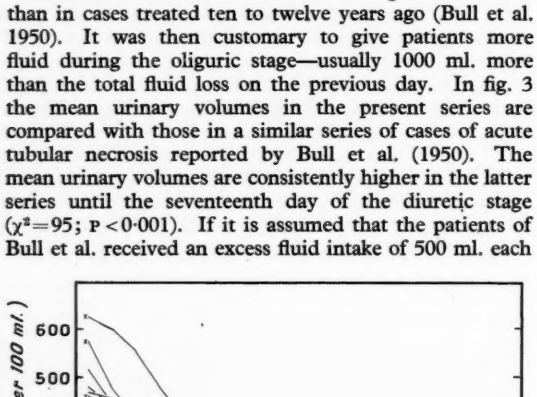

Fig. 4—The actual fall of blood-urea in 20 cases of acute tubular necrosis during the late diuretic stage. Crosses indicate cases treated by hæmodialysis.

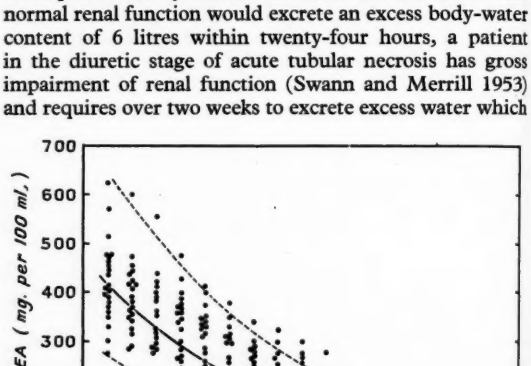

Fig. 5—The fall of blood-urea during the late diuretic stage of acute tubular necrosis. The logarithmic regression-line and limits at twice the standard deviation are shown.

During the late diuretic stage there is a progressive exponential fall in the blood-urea (figs. 4 and 5). On an average, the blood-urea becomes normal within seventeen days (fig. 5).

Convalescent Stage

By the end of the late diuretic stage the patient has passed through a long and serious illness which has lasted on an average five weeks (fig. 6). During this period there has been little or no intake of protein. Although modern conservative therapy reduces endogenous protein breakdown, often to a value as low as 40 g. per day, five weeks of protein starvation causes a loss of at least 1·5 kg. of body-protein—about an eighth of the total body content. The majority of this endogenous protein is derived from voluntary muscle. The patient at the start of the convalescent stage is still an invalid, characteristically weak and often unable to stand or walk unaided. Further recovery, however, is very rapid; the patient usually develops an insatiable appetite and quickly gains weight with increase of muscle mass and restoration of muscle

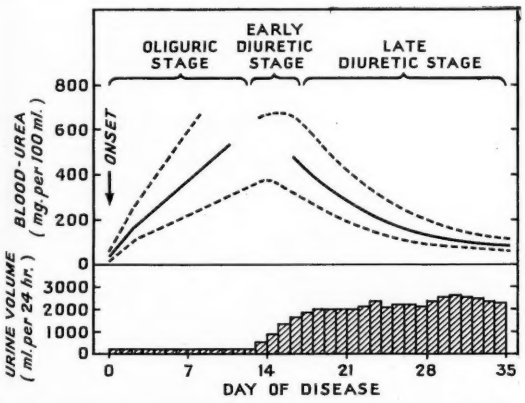

Fig. 6—Graphical representation of an average case of acute tubular necrosis which summarises the previous charts.

The regression-lines of blood-urea and the upper limit at twice the standard deviation for the oliguric and late diuretic stages are not continuous in this series, because many of the patients were treated by hæmodialysis in the last few days of the oliguric stage.

strength. Usually it is at least two or three months from the start of the illness before the patient is well enough to resume full activities and duties.

CLINICAL COURSE OF FATAL CASES

Of the 11 fatal cases (table II) originally diagnosed as uncomplicated tubular necrosis, all were examined at necropsy. 3 cases, all due to concealed accidental hæmorrhage of pregnancy, were found to have had severe bilateral renal cortical necrosis causing irreversible renal damage. We prefer to avoid percutaneous renal biopsy during the oliguric stage of acute renal failure, and therefore have no means of differential diagnosis between renal tubular necrosis and renal cortical necrosis except the response to therapy. The apparent mortality in this series was therefore 28%, but the true mortality excluding the cases of renal cortical necrosis was 22%—a figure similar to those in other reported series.

Of the 8 fatal cases of acute tubular necrosis, 4 died in the oliguric stage, 2 in the early diuretic stage, and 2 in the late diuretic stage. They showed no obvious biochemical differences from the patients who survived, and the oliguric stage of the 4 patients who died in the diuretic stage was not unusually long. Table II shows that sepsis, usually from organisms resistant to most available antibiotics, was the main cause of death.

Of the 3 fatal cases of renal cortical necrosis 2 also died as a direct result of infection, although the severity of their renal lesion would have precluded final recovery. 2 of these 3 patients died in the oliguric stage, on the ninth and eighteenth days. The 3rd patient passed into an early diuretic stage on the twentieth day of her illness, and the urine output rose to a maximum of 970 ml. per day before death on the twenty-ninth day. This shows that a guarded prognosis should be given in all cases of acute oliguric renal failure due to concealed accidental hæmorrhage of pregnancy, unless the patient has passed into the late diuretic stage with a steadily falling blood-urea. Even if percutaneous renal biopsy in such cases showed only acute tubular necrosis, this would not preclude renal cortical necrosis in other parts of the kidneys.

Discussion and Summary

The average course of uncomplicated acute tubular necrosis is summarised in fig. 6. Average durations of the first four stages of the disease are plotted on the abscissa, and the blood-urea and mean urinary volumes on the ordinate. The regression-lines for blood-urea and the upper limits at twice the standard deviation for the oliguric and diuretic stages are not continuous because almost half the patients were dialysed at the end of the oliguric stage. Hæmodialysis artificially reduces the blood-urea at the start of the early diuretic stage. It is almost certain that some of the patients would not have survived had hæmodialysis not been applied. Since the rate of climb of the blood-urea during the oliguric stage is identical before and after dialysis (figs. 1 and 2), it is permissible to extrapolate the rise of blood-urea after dialysis to that before treatment in order to estimate the eventual level had dialysis not been carried out. In the 2 patients who required dialysis on two separate occasions, the blood-urea would have been expected to rise to 1020 and 1110 mg. per 100 ml. Although in isolated cases recovery has followed the recording of similar levels of blood-urea, most such patients will die without hæmodialysis.

This paper may prove useful to those responsible for the decision to transfer cases of acute tubular necrosis to a centre with facilities for hæmodialysis. Although the duration of the oliguric stage in any single case remains unpredictable, the course of the oliguric stage may be accurately predicted after only a few days' careful observation. The course of cases with severe tissue damage cannot be predicted. Deterioration may be extremely rapid, and in these cases a high plasma-potassium or a low plasma-bicarbonate may provide urgent reasons for hæmodialysis before the blood-urea exceeds 400 mg. per 100 ml.

Thanks are expressed to Prof. G. M. Bull for permission to publish urinary volumes of patients under his care, and to Prof. J. McMichael and Prof. E. J. King for advice.

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CRYPTOGENIC LIVER ABSCESS

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LIVER abscess is uncommon in Great Britain. Between 1950 and 1958 only 8 cases have occurred in 14,500 admissions to the Hospital for Tropical Diseases (U.C.H.), giving an incidence of 0·055%. All these were shown to be amœbic in origin.

With a chronic abscess in a patient at risk for amœbiasis it is sometimes difficult to be certain whether amœbæ were initially responsible for it and whether their presence has been obscured by superadded bacterial infection. There is a growing feeling, however, that pyogenic infection is becoming more important as a primary cause even in tropical practice (Worms 1956), and this is supported by McFadzean et al.'s (1953) figures from Hong Kong.

During the decade 1949–58, 6 cases of liver abscess have

been seen in 183,000 admissions at University College Hospital in the general wards and in my private practice, giving an incidence of 0·003%. None of these patients was at risk for amœbiasis, no amœbæ were found in any case, and it seems certain that they were pyogenic in origin. This incidence agrees with de Bakey and Creech's (1956) estimate of 0·04–0·007% of all hospital admissions.

Pyogenic organisms may gain access to the liver:

1. From outside the body by trauma, which is self-evident.
2. Via the hepatic artery, in which case systemic blood-culture should be positive.
3. Via the bile-duct, when prominent early jaundice is to be expected.
4. Via the portal vein. In this group primary disease in the alimentary tract may be demonstrable (Dieulafoy 1898, Ochsner et al. 1938, Shallow et al. 1945, Champeau 1956), and a consideration of the venous drainage alerts the doctor to the possibility of hepatic spread.

Diagnostic difficulty arises when no primary lesion is apparent and the liver abscess itself produces the presenting symptoms. 4 of the 6 cases seen in the past decade fall into this group.

Case-records

Case 1.—A 78-year-old lady developed malaise, nausea, and vomiting on April 27, 1957. She had had appendicectomy for recurrent lower abdominal pain many years before, and had also suffered from cataract and allergic rhinitis, and had bilateral operations for carpal-tunnel syndrome. She was afebrile and there was no alteration in bowel habit, though other members of the household had recently had gastroenteritis.

When seen on May 4 she was mentally confused and clinically anæmic. Upper abdominal pain had appeared and there was slight tenderness across the epigastrium but no other abnormal physical signs. During the next fortnight fever appeared and she developed a leucocytosis of 20,000 (90% neutrophils). Her hæmoglobin fell from 88% to 70%. The erythrocyte-sedimentation rate (E.S.R.) was 52 mm. in first hour (Westergren). Blood-culture was sterile. Liver dullness was increased, though the edge of the liver was never palpable, and movement of the right diaphragm became reduced. X-rays showed a high right diaphragm and an enlarged liver shadow. She was never jaundiced. Her confusion increased to such a point that lumbar puncture was performed (demonstrating a normal cerebrospinal fluid) and a psychiatric opinion was taken before a diagnosis of liver abscess was made.

After preliminary treatment with penicillin and streptomycin, the upper part of the right lobe of the liver was explored on May 23 after resection of the 12th and 11th ribs. A soft area was found from which thin yellow offensive pus was aspirated. An abscess 2 × 2 in. was drained. Moderate numbers of gram-positive cocci and bacilli were seen in a smear of the pus, and it was thought that the lack of significant growth on culture after seven days indicated that these organisms were probably delicate anaerobes.

Her confusion disappeared and she made an uninterrupted recovery. She has since remained well.

Case 2.—A publican's 33-year-old wife had complained of right-sided abdominal pain for six weeks before she was seen on May 7, 1957. During this time she had been febrile on and off and feeling generally unwell. Her waist measurement had increased by 2 in. though her weight had decreased. She remembered having had a short attack of lower abdominal discomfort and diarrhœa four months previously, but her bowels had always been erratic. She had previously suffered from asthma and neurodermatitis and was highly strung.

She was ill and clinically anæmic, and there was muscular guarding and some tenderness in the upper abdominal quadrants, especially on the right, but there were no other abnormal signs. Her urine contained no pus and was sterile. Hæmoglobin 72%. White cells 10,400 (69% neutrophils), E.S.R. 54 mm. in first hour.

She declined admission to hospital till June 10, when her temperature had risen to 105°. She was very ill; the area of liver dullness was enlarged, but no liver edge could be felt. She became very slightly jaundiced (serum-bilirubin 1·8 mg. per 100 ml.) and the urine contained bilirubin. A few râles appeared at the right lung base and she was treated with penicillin and streptomycin. Flocculation tests were normal and blood-culture sterile.

She improved temporarily and her jaundice disappeared, but persistent pain, localising tenderness, increasing leucocytosis, and falling hæmoglobin (55%) led to a diagnosis of liver abscess in the anterior part of the right lobe. X-rays showed some elevation of the right diaphragm and enlargement of the liver shadow. This abscess was drained per abdomen in July, 1957, but she had a stormy postoperative course and further drainage was necessary twice.

Sinograms showed that the abscess extended high up into the anterior part of the right lobe (figs. 1 and 2). The pus grew a microaerophilic streptococcus and *Streptococcus fæcalis*. After the second recurrence of the abscess she was treated with prednisone in addition to appropriate antibiotics because the antibiotics might not be reaching the abscess cavity; her general condition had by this time improved a great deal and she was regaining her lost weight. On the tenth day of this treatment she had a brisk hæmatemesis which demanded transfusion, and a barium meal showed a large gastric ulcer half-way down the lesser curvature; this did not communicate with the abscess and had given no previous symptoms. Prednisone was stopped and she made a slow, steady recovery. Intravenous cholangiography with iodipamide methylglucamine ('Biligrafin') showed a normal biliary tract. She has since remained well.

Case 3.—A 74-year-old lady had been well until an unexplained attack of diarrhœa, probably infective, at the age of 71. When first seen on Oct. 7, 1958, she complained of anorexia, malaise, and fatigue for ten days, and pleuritic pain in the right lower chest for three days. She was ill and anæmic but not jaundiced. There were signs of aortic stenosis but no congestion of neck veins, though there was pitting œdema of both legs up to the knees. Liver dullness was increased, but the liver edge was not definitely felt and was not tender. There were signs of a small right pleural effusion and a friction rub high in the right axilla. Her temperature was 100°, hæmoglobin 52%, and white cells 15,000 (88% neutrophils). E.S.R. 76 mm. in first hour. X-rays showed a high right diaphragm and a small right pleural effusion which contained many white cells, predominantly lymphocytes, and was sterile.

She was transfused but remained very ill till Oct. 24, when she coughed up 100 ml. of foul-smelling pus which grew an

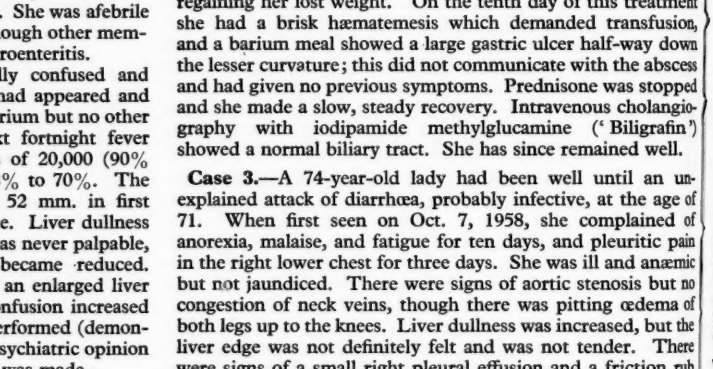

Fig. 1 Fig. 2

Fig. 1 (case 2)—Sinogram. Postero-anterior view showing abscess cavity.

Fig. 2 (case 2)—Sinogram. Lateral view showing position of the abscess cavity in the anterior part of the right lobe of the liver.

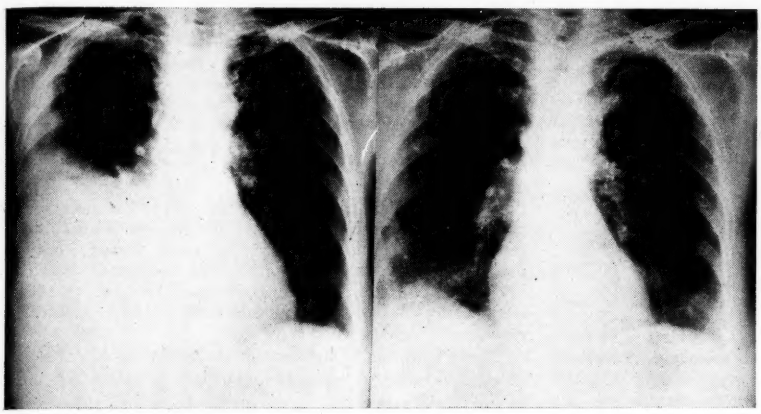

Fig. 3

Fig. 4

Fig. 3 (case 3)—Postero-anterior view of chest on Oct. 31 after the abscess had burst into the lung.

Fig. 4 (case 3)—Postero-anterior view of chest showing some residual shadowing in the right lower lobe with return of the diaphragm towards the normal position.

anaerobic streptococcus. It grew no tubercle bacilli and contained no cancer cells or amœbæ. She was treated with penicillin and streptomycin and postural drainage and became afebrile on Oct. 31 (fig. 3). Mental confusion, which had been a feature of her illness, gradually lessened and she made a slow, steady recovery, leaving hospital on Nov. 23.

When last seen on March 3, 1959, she had recovered her normal energy and was leading a very active life. Her hæmoglobin was 84%. A few râles could still be heard at the right base and the X-ray had not completely cleared (fig. 4). She had no cough but she probably has some residual fibrosis in the right lower lobe. She remains well.

Case 4.—A 61-year-old man had had an appendicectomy at 19 and had then remained well (apart from an attack of urinary infection at 58) till he developed fever, malaise, and anorexia in July, 1955. There was a slight pleural reaction at the right base and a leucocytosis of 19,700 (84% neutrophils). He recovered after a month in hospital but had to be readmitted on Nov. 11, 1955, because of malaise and upper abdominal pain. The liver was enlarged and tender, and over the next three weeks a mass continuous with the liver appeared in the right loin. Laparotomy showed this to be a large abscess in the right lobe of the liver; offensive pus, which grew anaerobic cocci, was drained through the loin. He made an interrupted recovery on penicillin and streptomycin and returned to work two months later.

Discussion

Pathogenesis

From the clinical standpoint all these abscesses were cryptogenic, though in retrospect there may have been slender clues to their site of origin in the diarrhœa previously sustained by case 2 and in the gastroenteritis of other members of the household of case 1.

de Bakey and Creech (1956) thought that about half of all pyogenic abscesses are cryptogenic. Rothenberg and Linder (1934) believed that they are caused by hæmatogenous spread from unrecognised distant systemic foci, while Beaver (1931) regarded them as the result of quiet infection in areas drained by the portal tract. The presence of anaerobic cocci in my four cases supports Beaver's concept; and it seems possible that intercurrent gastrointestinal infection can allow increased entry of gut bacteria into the portal system through an inflamed intestinal mucosa—these organisms occasionally gaining a foothold in the liver despite its liberal network of vascular anastomoses and abundant supply of phagocytes.

Diagnosis

Bourne (1954) has emphasised the importance of early diagnosis if high mortality is to be avoided.

Liver abscess should be suspected wherever there is fever of obscure origin accompanied by steady upper-abdominal pain. Examination will show enlargement of liver dullness, even though the liver edge may not be palpable. With an abscess in the upper part of the right lobe, the lower margin of the liver may be displaced downwards without becoming harder; and in determining the palpability of the liver edge firmness is more important than enlargement. There may be tenderness over the liver and pain may be produced by percussion over the right lower ribs or by firm pressure in the intercostal spaces in this region. Jaundice is absent, or slight and transient, as would be expected from a focal lesion of the liver not obstructing the main bile-ducts. By the same token there is no indication, clinical or biochemical, of hepatocellular failure. Mounting leucocytosis and a high right diaphragm afford supporting evidence, and, if the disease is firmly established, anæmia may follow.

Mental confusion may be prominent in older patients. This is a symptom which may be encountered in anyone of an advanced age with an acute infection, especially if he is anæmic. It deserves special mention since it was a leading symptom in case 1.

If diagnosis is delayed, the abscess may rupture into neighbouring organs—most often into the lower lobe of the right lung or pleural cavity as in case 3.

Treatment and Prognosis

Antibiotic treatment must be combined with adequate drainage. Ideally the organism should be cultured and its sensitivity determined; in this context the importance of anaerobic culture has been stressed in general by E. J. Stokes (1958) and in particular by Worms (1956). In practice, these cryptogenic abscesses so often yield anaerobic or micro-aerophilic cocci that penicillin and streptomycin, to which they are commonly sensitive, should not be withheld from an ill patient.

Surgical rather than spontaneous drainage is desirable. Ochsner et al. (1938) found that rupture into neighbouring organs worsened the prognosis, and the fatality-rate in their series, if such complications were excluded, was 36%, contrasting with the 50% rate estimated by Eliason (1926) for all cases in pre-antibiotic days.

The direct benefit of antibiotics and the greater safety they confer on surgical procedures are responsible for the better prognosis in these abscesses nowadays. Case 2 had much the stormiest passage and this can be related to the position of the abscess in the liver (fig. 2), which demanded transperitoneal anterior drainage. Ill recumbent patients cannot drain their abscesses anteriorly, and a posterior approach is preferable whenever possible.

Summary

Four cases of cryptogenic non-amœbic liver abscesses with recovery are described.

No primary source of infection was evident clinically. Anaerobic cocci were isolated from the pus in each case. An origin in the gut and spread via the portal vein is probable.

The organisms were all sensitive to penicillin and streptomycin. Recovery is attributed to the use of these drugs combined with effective drainage.

My thanks are due to Dr. E. E. Pochin for access to the records of case 4.

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A TRIAL OF BACTERIAL VACCINES FOR THE COMMON COLD IN THE ROYAL AIR FORCE

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MANY attempts have been made to prepare bacterial vaccines for the prevention or attenuation of the common cold. Their use has been based on the assumption that the stage of secondary infection might thereby be eliminated or reduced in severity. Most of these vaccines have been prepared from mixtures of selected organisms, chosen because of their supposed pathogenicity.

Of the numerous trials of such vaccines, the few in which controls were adequate have given disappointing results.

Diehl et al. (1938) made a carefully controlled study of three vaccines, one administered subcutaneously and two orally, with randomly selected controls receiving a placebo. The group which received the subcutaneous vaccine had 25% fewer colds per person than the control group, but the groups receiving oral vaccines showed no advantage over the controls. Diehl et al. concluded that the vaccines had little or no practical value. McGee et al. (1944), in a well-controlled trial of two vaccines administered parenterally and three oral vaccines, found no clear evidence of a reduction in either the frequency or the severity of the common cold.

In 1958, however, Ritchie reported a controlled trial in which autogenous bacterial vaccines reduced the severity of colds and the time lost from work due to colds and upper-respiratory infections in a group of factory workers.

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Throat and nose swabs and specimens of saliva were collected from all volunteers. When the subject was included in the randomly selected group to be given vaccine, the vaccine was prepared from the whole mixed culture of these specimens; when he was to be a control the specimens were discarded and he was given injections of carbol saline instead. Injections were given weekly for up to five months during the winter, but for administrative reasons about half the volunteers stopped having injections after 8 weeks, although records of their colds continued to be made to the end of the trial. The numbers of colds in the inoculated and control groups were similar, but in the vaccinated group only 13% of colds passed from the prodromal to the fully developed stage, compared with 62% in the control group. There was evidence, however, that those who did not continue with the injections lost fairly rapidly the resistance which they had acquired.

These findings, if substantiated, might be of considerable importance to certain groups such as flying personnel in the Royal Air Force in whom the duration and severity of colds is a matter of concern. It was decided, therefore, to conduct a trial in the R.A.F. based on Ritchie's method, but modified to meet the practical demands of the situation. The vaccines were prepared in the same way as Ritchie had prepared his, but the dosage schedule was modified, as weekly injections would not be welcomed by healthy men and would be difficult to arrange on an operational flying station. Furthermore there seemed to be no theoretical reason why weekly injections should produce a better immunological response than a more usual course. In addition to those receiving individual autogenous vaccines and a control group given phenol saline, a third group was given a " pool " vaccine prepared by mixing the culture washings from all the members of the group.

Clinical and Laboratory Methods

Selection of Subjects

The trial took place between October, 1958, and the end of March, 1959, at R.A.F. College, Cranwell, and at R.A.F. Stations Oakington and Thorney Island. Volunteers were obtained from among flying cadets and instructors, since they would be keen to cooperate in a measure which might help to keep them flying, and because they are kept under close medical supervision, particularly with regard to respiratory infections. The importance of reporting all colds, however minor, to the medical officer before flying is constantly stressed and therefore complete records could be hoped for. About a dozen non-flying officers were also included, but they were treated for the purposes of the trial as if they had been fliers. All volunteers were told that some of them would receive a vaccine which might reduce the loss of flying-time due to colds and that some would receive an inert control, but that they would not know till after the trial which they had received.

Method of Vaccine Preparation

A single swab was used to sample the tonsillar region and the front of the mouth of each man. The swabs were inoculated over the whole of a blood-agar plate. After overnight aerobic incubation at 37°C the plates were inspected. Eight of those allocated to the autogenous-vaccine group and nine of those in the pool group showed a heavy growth of hæmolytic streptococci; to lessen the risk of reactions, men yielding these cultures were transferred to the control group and replaced in the appropriate vaccine group by randomly selected men whose cultures did not show hæmolytic streptococci. The growth on each plate from the men in the two vaccine groups was then washed off with normal saline containing 0·5% phenol and diluted separately with the phenol-saline to an opacity corresponding to a strength of about 500 million per ml. A pool vaccine was constituted in the same way by mixing the washings from all the men in the appropriate group. The vaccines were heated in a water-bath to 60°C for 1 hour and each was tested for sterility by inoculating 0·5 ml. into a tube of

thioglycollate broth. The vaccines and the phenol saline were put into individual exactly similar vaccine bottles for each volunteer.

Inoculation Procedure

A total of 320 volunteers was allocated to the groups to receive autogenous vaccine, pool vaccine, or phenol saline, by reference to a table of random numbers. Each group was treated in an exactly similar manner. Neither the volunteer nor the medical officer giving the injections was aware of what was being given. Injections were given into the deep subcutaneous tissues of the upper arm, a separate, dry-sterilised syringe being used for each subject. The first dose, which was given in early October, 1958, was of 0·1 ml.; the second dose a week later was 0·3 ml.; the third dose, two weeks after the second, was 0·5 ml.; a fourth, reinforcing dose, also 0·5 ml., was given in mid-January, 1959. On a personal record card, which was prepared for each man, were noted the dates of his injections and reactions to them. Two men who had originally been in the autogenous-vaccine group were given pool vaccine for the reinforcing dose because their bottles of vaccine had been damaged.

Reactions to Inoculation

Reactions were generally trivial. After each of the injections about a third of those receiving the autogenous or pool vaccines and a few of the controls had slight redness, swelling, and soreness at the injection site for 24–48 hours. In the autogenous vaccine group 2 men had more severe local reactions with an accompanying local lymphadenitis, 1 of them after both the second and the third injections and the other after the reinforcing dose only. In the pool vaccine group 1 man had a severe local reaction accompanied by mild general malaise following the reinforcing dose. There were a few mild general reactions after each of the injections in the pool and autogenous groups but none in the control group. 1 man in the autogenous-vaccine group experienced symptoms similar to allergic rhinitis starting 6–9 hours after each of the first three injections and clearing up in 48 hours; owing to release from the Service he did not have a reinforcing dose.

Recording Methods

Volunteers were urged at the beginning of the trial and reminded at intervals to report to their medical officer all respiratory infections however mild they might be. In this way, and because all flying personnel are well aware of the dangers of flying with a cold, it is believed that reasonably complete records were obtained. The assessment and the record of each illness were made by the station medical officers. As stated above, neither they nor the volunteers knew who had received the vaccines and who the saline control. The date of each illness reported and the diagnosis were noted on the back of the personal record card. To support this entry an illness record card was completed for each illness. On one side of this card were recorded certain features of the severity of the illness, including the number of days off full flying duties, a diagnosis, and an assessment of whether the illness was mild, average, or severe, taking into account both diagnosis and the patient's usual experience. The number of days off full flying duties included weekends, and where the man was on leave or off flying duties for any other reason the number of days that he would have been off duty was assessed. On the reverse side of the card were recorded the presence and severity of the following symptoms and signs within 48 hours of onset and after 48 hours: nasal discharge, sinus pain, postnasal drip, cough, sputum, and negative Valsalva sign. When a volunteer was absent from the station or omitted to report an illness when it occurred, a record card was completed as far as possible in retrospect. Uniformity in the compilation of records between the units taking part was ensured as far as possible by monthly visits to each of the stations.

Of the 320 original volunteers, 293 received all three initial injections and were followed for at least 1 month after the third dose. These were considered to be the minimum qualifications for inclusion in the final assessment of results. A further 17 volunteers left their stations at various times during the subsequent course of the trial, and another 8 men did not receive the reinforcing dose for various administrative reasons. Owing to these losses and also to some variation in the dates of injection the total period of follow-up tended to vary slightly with individuals, but it was found that the total numbers of weeks of exposure in each of the two vaccine groups and the control group were almost identical. Therefore the slight variations in the numbers and periods of follow-up were ignored.

TABLE I—INCIDENCE OF ALL RESPIRATORY ILLNESSES
(Attack-rates (%) in parentheses)

—	Autogenous vaccine	Pool vaccine	Control group
Total no. of volunteers	99	97	97
Total no. of illnesses	116 (117%)	119 (123%)	124 (128%)
Illnesses 3–6 weeks (incl.) after 3rd and reinforcing doses:	34 (34%)	53 (55%)	52 (54%)
Illnesses during remainder of trial	82 (83%)	66 (68%)	72 (74%)
Illnesses 1–2 weeks after 3rd and reinforcing doses:	43 (43%)	33 (34%)	28 (29%)
Illnesses during remainder of trial	73 (74%)	86 (89%)	96 (99%)

Results

The sickness records were analysed separately for the incidence and severity of all respiratory infections during the total period from the last of the three initial doses of vaccine to the end of the trial, and for two shorter periods within this time: (1) the period when the maximum effect of a normal immunological response would be expected, 3–6 weeks after inoculation; and (2) the period when the effects of any immediate but shortlived immunity would be expected, in the first 2 weeks after inoculation.

TABLE II—NUMBER AND PROPORTION OF ILLNESSES CLASSIFIED AS MILD

Illnesses	Autogenous vaccine	Pool vaccine	Control group
Total	51 (44%)	51 (43%)	50 (40%)
3–6 weeks (incl.) after 3rd and reinforcing doses:	10 (29%)	24 (45%)	17 (33%)
During remainder of trial	41 (50%)	27 (41%)	33 (46%)
1–2 weeks after 3rd and reinforcing doses:	21 (49%)	9 (27%)	12 (43%)
During remainder of trial	30 (41%)	42 (49%)	38 (40%)

Table I shows the sickness incidence for all respiratory illnesses during the periods defined above. The total illness-rates in the three groups were about the same, but during the period from the 3rd to the 6th weeks after inoculation those in the autogenous-vaccine group had significantly fewer illnesses than the controls.

$$\left(\frac{\text{Difference}}{\text{Standard error}} = \frac{20}{7} = 2{\cdot}9\right).$$

On the other hand the sickness-rates in the autogenous-vaccine group were higher than in the controls during the remainder of the trial.

Table II shows the proportions of illnesses which were classified as mild. There was little difference in the severity of illnesses in the three groups shown by this method of assessment in each of the selected periods.

TABLE III—NUMBER AND PROPORTION OF ILLNESSES INVOLVING THE LOSS OF MORE THAN 3 DAYS' FLYING-TIME

Illnesses	Autogenous vaccine	Pool vaccine	Control group
Total	54 (47%)	64 (54%)	68 (55%)
3–6 weeks (incl.) after 3rd and reinforcing doses:	18 (53%)	24 (45%)	28 (54%)
During remainder of trial	36 (44%)	40 (61%)	40 (56%)
1–2 weeks after 3rd and reinforcing doses:	14 (33%)	20 (61%)	15 (54%)
During remainder of trial	40 (55%)	44 (51%)	53 (55%)

TABLE IV—NUMBER AND PROPORTION OF ILLNESSES IN WHICH PURULENT SYMPTOMS OR SIGNS PERSISTED MORE THAN 48 HOURS FROM ONSET

Illnesses	Autogenous vaccine	Pool vaccine	Control group
Total	54 (47%)	66 (55%)	68 (55%)
3–6 weeks (incl.) after 3rd and reinforcing doses:	13 (38%)	27 (51%)	26 (50%)
During remainder of trial ..	41 (50%)	39 (59%)	42 (58%)
1–2 weeks after 3rd and reinforcing doses:	19 (44%)	16 (48%)	19 (68%)
During remainder of trial ..	35 (48%)	50 (58%)	49 (51%)

It was particularly relevant to this study to know whether the volunteers who were vaccinated lost less flying-time than the controls. Table III shows that they did not, except to a small degree during the first 2 weeks after inoculation with autogenous vaccine.

If the vaccine were effective in shortening the stage of secondary infection of colds, fewer of the vaccinated persons would be expected to show purulent symptoms lasting more than 48 hours from onset than the controls. In fact, as is shown in table IV, this was so for those receiving the autogenous vaccine, mainly in the period immediately following inoculation but also to some extent in the period 3–6 weeks after inoculation, although in neither instance was the reduction very great.

Illnesses diagnosed as common cold formed 86% of the total and were almost equally distributed among the two vaccine groups and the controls. All results were substantially the same when these illnesses were considered separately.

Comment

It is clear from these results that autogenous bacterial vaccines as administered by us are unlikely to have any practical application in dealing with the problem of the common cold among flying personnel of the Royal Air Force. There was, however, an interesting reduction in the incidence of illness in the autogenous-vaccine group in the period when it might be expected, between the 3rd and 6th weeks after inoculation. Although there is little supporting evidence of reduced severity or duration of those colds which were reported during this period, there was some reduction in the number in which purulent symptoms persisted. These observations are difficult to explain, since a vaccine designed to prevent secondary bacterial infection would be expected to reduce the severity of illnesses rather than their incidence. Possibly, however, the reduction in severity of some colds was such that it led to under-reporting of these mild incidents. Our results thus stand in contrast to those of Ritchie; but our volunteers received only four injections, whereas his were given them weekly for at least 8 weeks and many for the whole winter. It is also possible that flying personnel of the R.A.F., who are carefully selected on medical grounds, suffer less from the bacterial complications of the common cold than factory volunteers, a proportion of whom were subject to heavy colds. Autogenous bacterial vaccines, perhaps in greater dosage, may therefore merit further investigation among less healthy persons.

Summary

A controlled trial of autogenous bacterial vaccines for the common cold among 293 flying personnel of the Royal Air Force is reported. Three groups were formed and given autogenous vaccine, a pool vaccine, or phenol saline in a course of three initial doses in October, 1958, and a reinforcing dose in January, 1959. The volunteers were observed until the end of March, 1959, and records were made of all their respiratory infections during this time.

The total incidence and severity of respiratory illnesses in the three groups were very similar; and such vaccines are, therefore, unlikely to have any practical application to the problem of the common cold among flying personnel of the Royal Air Force. There was, however, a statistically significant reduction in the illness attack-rate in the autogenous-vaccine group during a limited period of 3 to 6 weeks after the third and reinforcing doses.

Our thanks are due to the medical officers at R.A.F. College, Cranwell, and at R.A.F. Stations Oakington and Thorney Island for their valuable cooperation and assistance with every stage of this investigation, and to the Director-General of the Royal Air Force Medical Services for permission to publish the results.

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DYSPEPSIA DUE TO INHALATION OF CARBON TETRACHLORIDE VAPOUR

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PATIENTS often blame their work for their indigestion, though this symptom is rarely directly attributable to occupation. Any common symptom may, however, arise from work and the connection may be missed unless one asks in detail what are the actual processes involved. Even then the patient may be unaware of the toxic nature of the materials that he uses, and the poison responsible may play a minor role in the main process on which he is engaged.

A man of 34 years of age attended Poplar Hospital complaining of anorexia, nausea, and occasional vomiting with a feeling of abdominal discomfort not amounting to pain. He had had these symptoms intermittently for two years, and on this occasion for about two months, during which time he felt unusually depressed and irritable. No abnormal signs were found on clinical examination.

One odd feature in the history—that the dyspepsia was better at weekends and built up during the week—led to more detailed inquiry about the patient's work. It was then found that he was exposed to the vapour of carbon tetrachloride, and that other workers had developed similar symptoms in the past few months and some had consulted their doctors. A visit to the factory was arranged.

Description of the Factory

There were 18 people—14 men and 4 women—employed in a workshop with an area of about 3000 sq. ft., divided into two parts by a wooden partition which did not reach the roof. The windows were kept closed, and there was no mechanical ventilation. The room was heated by indirect gas convector heaters, each of which was connected to a flue passing through the roof. On entering the room one could detect no atmospheric contaminant, but one could smell carbon tetrachloride in the immediate environment where it was used.

Process

The factory processes raw quartz in the manufacture of crystals for electronic equipment. The quartz is examined for flaws, before being orientated and cut with diamond-impreg-

nated saws. After X-raying and further cutting, the crystal blanks are stuck by means of a resinous wax on to lapping plates and ground on carborundum. The crystals are cleaned in carbon tetrachloride to remove the resinous wax; etched with hydrofluoric acid; then further cleaned by being passed through solutions of chromic acid, distilled water, methylated spirit, and acetone; and finally dried in an oven. The crystals are adjusted to their correct frequency by the addition of gold, effected by electroplating in a gold-cyanide solution. Finally, the crystals are mounted and cleaned by being passed through the series of solvents again, starting with carbon tetrachloride. To facilitate the cleaning process, an ultrasonic vibration of about 40,000 cycles per second is passed through the carbon tetrachloride solution. About two Winchester quarts (five litres) of carbon tetrachloride are used weekly, although much of this is thrown away.

When a beaker of carbon tetrachloride was placed in the ultrasonic cleaning apparatus, drops of carbon tetrachloride could be seen spraying out from the beaker, and the characteristic odour of its vapour was obvious. Carbon tetrachloride could also be smelt in the vicinity of another bench, where the plates were cleaned with cloth dipped in the solvent.

Clinical Survey

Medical and occupational histories were taken from 17 of the 18 employees, and 16 of the 17 workers interviewed were examined clinically.

Of the 17 workers seen, 15 complained of symptoms, which are shown in table I. The pattern was similar in all. Nausea was usually first noticed on a Tuesday or a Wednesday afternoon and increased in severity as the week progressed. Anorexia was most severe for the evening meal. These symptoms were accompanied in most cases by upper abdominal discomfort, which did not amount to pain, but was described as an unpleasant distended feeling. The incidence of vomiting was more varied. In the more severe cases vomiting occurred up to four times in the day, usually on a Thursday or a Friday, and took place both at work and at home in the evenings.

Of the remaining symptoms, depression was the most pronounced, and this was noticed by workers who had never had such feelings before. Complaints were made of irritability and of unusual shortness of temper with children at home. There were no complaints of lassitude or somnolence. In all but 2 of the workers the symptoms had first manifested themselves during the preceding four months, since the autumn of 1958, and were most severe in the weeks prior to our visit. This coincided with the closure of windows in the colder weather.

The clinical examinations were performed five days after precautions had been taken to reduce further exposure. No abnormal physical signs were discovered. The fundi and visual fields were normal. 3 men had mild upper abdominal tenderness, but without guarding. No abnormalities were found in the urine. Case 7 (table I) when originally examined in hospital had a raised serum-glutamic-oxalate-transaminase (76 units per ml.), but this test was normal in this man and in 7 others at the time of the clinical examinations.

TABLE II—ATMOSPHERIC CONCENTRATION OF CARBON TETRACHLORIDE IN DIFFERENT SITES IN THE WORKSHOP AFTER RUNNING THE ULTRASONIC EQUIPMENT FOR THREE HOURS: (*a*) BEFORE COVERING BEAKERS CONTAINING CARBON TETRACHLORIDE; (*b*) AFTER COVERING THE BEAKERS

Site	Concentration of carbon tetrachloride			
	Before covering beakers		After covering beakers	
	Parts per million	mg. per c.m.	Parts per million	mg. per c.m.
Adjacent to ultrasonic apparatus:				
Bench 1	97	620	8	50
Bench 2	70	450	9	60
Bench 3	67	430	0	0
On other side of partition:				
Bench 4	45	290	<8	<50
Bench 5	47	300	<8	<50
Bench 6	45	290	<8	<50

Environmental Survey

The concentration of carbon tetrachloride in the atmosphere at different sites in the workshop was estimated after the ultrasonic equipment had been running continuously for three hours, and repeated after the control measures suggested were put into practice. The atmospheric samples were taken into two impingers in series with a handpump, carbon tetrachloride in the samples being estimated by the technique described by Strafford et al. (1956). The results obtained at various sites in the workshop are given in table II. A maximum allowable concentration in the atmosphere of carbon tetrachloride of 25 parts per million (160 mg. per c.m.) was recommended by the American Conference of Governmental Hygienists (1959). The concentrations obtained under the original conditions were considerably in excess of this recommended figure, as can be seen in table II, which also shows the effectiveness of the simple control measures instituted. The beakers containing carbon tetrachloride were covered, and the cleaning of plates with cloth dipped in carbon tetrachloride was stopped. All the workers were symptom-free within one week, and there were no recurrences up to six months later.

Discussion

That exposure to high concentrations of carbon tetrachloride produces narcosis, liver damage, and kidney damage is well known. It is less well known, however, that exposure to lower concentrations may be responsible for less serious effects. In a detailed investigation of workers subject to prolonged exposure to carbon tetrachloride, Stewart and Witts (1944) found a high incidence of gastrointestinal upset and mental hebetude. The symptoms were similar to those in our patients with the difference that diarrhœa was prominent in their group. Their radiological investigations showed hypermotility with accompanying irritability and irregular contraction throughout the alimentary tract, and they suggested that these effects were produced by autonomic

TABLE I—SYMPTOMS PRESENT IN 17 WORKERS EXPOSED TO CARBON TETRACHLORIDE

—	Case no.																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age (yr.)	43	32	27	33	44	26	34	29	54	31	24	16	17	53	23	42	27
Symptoms:																	
Nausea	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−
Anorexia	−	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	−
Vomiting	−	−	−	+	+	+	+	+	−	−	−	+	−	−	+	−	−
Flatulence	+	+	−	−	+	+	−	−	−	+	−	+	−	−	+	−	−
Epigastric discomfort or distension	+	+	+	+	−	+	+	−	−	+	+	−	−	+	+	−	−
Depressive symptoms, headache, giddiness	+	+	+	+	+	−	+	−	−	+	−	+	−	+	+	−	−
Duration of symptoms (mos.)	4	4	2–3	2	2	24	24	2–3	0	½	2½	2	¼	2–3	1½	2½	0

stimulation. They found no evidence of liver damage on liver-function tests, and they disputed the view of Elkins (1942) that such symptoms reflected an early stage of liver damage.

Stewart and Witts were unable to measure atmospheric concentrations of carbon tetrachloride. Smyth and Smyth (1936), on the basis of animal experiments and clinical studies, concluded that 100 parts per million of carbon tetrachloride in the atmosphere would be a reasonable maximum allowable concentration. This figure has steadily fallen over the years to the present American level of 25 parts per million. The findings presented here show that a concentration of carbon tetrachloride in the working environment of the order of 45–100 parts per million can be associated with the appearance of symptoms of poisoning.

Summary

A group of factory workers developed nausea, and other symptoms increasing in severity in the latter half of each working week. These symptoms were attributed to exposure to the vapour of carbon tetrachloride in a concentration of approximately 45–100 parts per million.

We wish to thank Dr. Donald Hunter and Dr. A. I. G. McLaughlin for their advice; and Mr. E. King, Mr. P. N. Casbolt, and Mr. D. E. Fine, of the Department for Research in Industrial Medicine, Medical Research Council, for carrying out the atmospheric sampling and analyses.

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POLYNEURITIS AND CENTRAL HYPERTENSION DUE TO NON-PAROTITIC MUMPS

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THE nervous system is not infrequently involved in infections with the mumps virus. A short, benign, lymphocytic meningitis is the commonest neurological complication of the disease and has been reported in as many as a third of infected patients (Holden et al. 1946, Brown et al. 1948). It may cause no symptoms and be detected only by routine examination of the cerebrospinal fluid.

Involvement of the nervous system usually follows the development of clinically obvious parotitis within a period of a week. Occasionally the parotitis may be delayed.

Eberlein and Lynxwiler (1947) showed, in a review of 280 cases of mumps "meningoencephalitis" reported since 1918, that in about 10% of cases the neurological illness antedated the parotitis by several days. In a further 13% of cases clinically evident parotitis did not occur at any stage of the illness. In most instances the diagnosis was based on the occurrence of the characteristic neurological illness during epidemics of mumps, or in close contacts of known cases of parotitis. In the more recent cases the diagnosis was based on the development, in patients with meningoencephalitis, of diagnostic changes in mumps antibody titre (Kane and Enders 1945). The occurrence of meningoencephalitis due to serologically proven mumps, without parotitis, is now well documented (Enders 1946, Kilham et al. 1949, Kilham 1949, Adair et al. 1953, Horstmann 1956, Overman 1959).

Involvement of the nervous system may on occasion show itself in the course of mumps by conditions other than meningitis. Facial palsy, labyrinthitis, nerve deafness, and other localised forms of neuritis are well-known complications. Encephalitis and myelitis, clinically and pathologically very similar to the parainfectious encephalomyelitis due to measles, rubella, and varicella (Miller et al. 1956) may occur.

Polyradiculitis and polyneuritis are extremely rare complications of mumps. Miller et al. (1956) could find only 9 cases reported between 1934 and 1956. Parotitis was present in every case, although in 3 instances it developed only after the onset of neurological symptoms.

No cases appear to have been described hitherto of nonparotitic mumps presenting as polyneuritis. We here report such a case, which had two further most unusual features—namely, severe and fairly long-continued hypertension of "central" origin and the onset of meningoencephalitic symptoms well after the development of frank polyneuritis. Although "central" hypertension is a well-known feature of certain cases of bulbar poliomyelitis and has been reported in "acute infective polyneuritis" (Woltman and Kernohan 1955) it does not appear to have been previously described in "allergic" parainfectious polyneuritis or polyradiculitis.

Case-report

Mrs. A, aged 17, was admitted to Queen Charlotte's Hospital in the 32nd week of her first pregnancy and treated with streptomycin on account of a urinary infection. Throughout this pregnancy her blood-pressure never rose above 130/80 mm. Hg. On Dec. 30, 1958, she gave birth, at term and by normal delivery, to a $6^1/_2$ lb. boy. On the second day of the puerperium mild pyrexia developed, and this persisted for two weeks. On the eighth day she complained of "pins and needles" in her hands and feet and of an unsteady gait. She was found to have absent reflexes in the lower limbs and slight sensory impairment in both feet.

Apart from rheumatic fever in childhood she had always been healthy. There was no personal or family history of epilepsy. There had been no recent contact with any case of mumps.

Investigations

The patient had mild normocytic anæmia (Hb 75%) and total white blood-cells 12,500 per c.cm. The Paul-Bunnell test was negative and blood-cultures were sterile. The urine contained a trace of albumin and yielded a scanty growth of coagulase-negative *Staphylococcus albus*. The blood-urea was 23 mg. per 100 ml. The cerebrospinal fluid (C.S.F.) was under normal pressure but contained 140 mg. of protein per 100 ml.; the cell count and sugar content were normal and the fluid was sterile on culture.

On the basis of the clinical findings and of the albuminocytological dissociation in the C.S.F., Guillain-Barré syndrome was diagnosed.

Course

On the thirteenth day of the puerperium the patient had nine very severe generalised convulsions within a period of fourteen hours, and she remained unconscious for forty-eight hours. For the first time her blood-pressure was found to be raised (180/130 mm. Hg). White blood-cells had now increased to 18,000 per c.mm. The serum-electrolytes were normal and the urine contained 13 mg. of protein per 100 ml. and grew a β-hæmolytic streptococcus on culture. A further lumbar puncture yielded C.S.F. containing 150 mg. of protein per 100 ml., but only 1 lymphocyte per c.mm.

The fits were treated with paraldehyde and chlorpromazine, and the patient was subsequently given sodium phenytoin (50 mg. b.d.). Lactation was suppressed by three injections of 15 mg. of stilbœstrol, given on successive days, and the urinary infection was treated with a five-day course of chloramphenicol. Her blood-pressure remained persistently raised at 180/130 mm. Hg, and treatment with reserpine (0·25 mg. b.d.) was started.

During the following week her level of consciousness improved, but severe paralysis of the limbs developed. In view of this, the associated convulsions, and the persistently raised blood-pressure, she was transferred to Hammersmith Hospital on Jan. 19, 1959.

Condition on Transfer

On admission the patient complained of severe occipital headache, double vision on looking to the left, circumoral parasthesiæ, and slight difficulty with speech and swallowing. She was unable to move her limbs and could not turn about in bed. There were no paræsthesiæ in the limbs. Sphincter control was not impaired. Temperature 98°F; no rash, lymphadenopathy, enlargement or tenderness of the salivary glands, or sternal tenderness; body-weight 84 lb. Pulse-rate 120 per minute; blood-pressure 200/120 mm. Hg.

The patient was apathetic and had mild meningism. The fundi were normal. She had bilateral external rectus pareses, coarse nystagmus on looking to the right and fine nystagmus on looking to the left, and some rotatory nystagmus on upward gaze; bilateral facial paresis; and mild bilateral palatal and pharyngeal palsies. There was severe generalised symmetrical wasting of the upper and lower limbs with much associated weakness, especially distally, and moderate weakness of the trunk muscles.

The muscles were tender and there were early contractures at the right elbow and ankle. All the tendon reflexes were absent. The plantar responses were feebly flexor. There was impairment of light touch and pain sense, and loss of vibration and postural sense in the hands, forearms, feet, and legs of "glove-and-stocking" distribution.

Further Investigations

The blood picture was normal. The erythrocyte-sedimentation rate was 25 mm. in the first hour (Westergren). The Paul-Bunnell test was again negative. Serum-electrolytes, blood-urea, and liver function tests were normal. The urine contained no albumin, porphyrins, or other abnormal constituents and was sterile on culture. The Mantoux test was negative at 1 : 10,000. The C.S.F. contained 490 mg. of protein per 100 ml. but was otherwise normal. An intravenous pyelogram was normal.

An electroencephalogram (E.E.G.) on admission showed a severe generalised abnormality with no normal rhythms present. It was dominated by very large bilaterally synchronous slow waves, most prominent precentrally and occasionally of higher amplitude on the right side.

As no obvious factors had been discovered to account for the polyneuritis and subsequent meningoencephalitis, serum was sent to the Central Public Health Laboratory, Colindale. At no stage were abnormal titres of antibodies against any of the known "respiratory" viruses found, but the following results were unexpectedly obtained:

Date (1959)	*Day of disease*	*Mumps: "virus particle" antigen*	*Mumps: "soluble" antigen*
Jan. 13	6	1/32	1/16
„ 23	16	1/64	1/32
Feb. 19	43	1/8	1/8
March 13	65	1/8	1/8

These findings were interpreted by Dr. C. E. D. Taylor, of the routine diagnostic laboratory, Colindale, as strongly suggestive of recent infection with mumps virus. The serum-amylase was normal.

Progress

The patient was given phenobarbitone (50 mg. t.d.s.) and sodium phenytoin (100 mg. t.d.s.); this was gradually reduced *pari passu* with the improvement in the E.E.G. findings and was finally stopped when these findings had returned to normal. She received regular physiotherapy.

Two days after admission to Hammersmith Hospital she had two further generalised convulsions, each lasting about two minutes, in which the only lateralising features were deviation of the head and eyes to the right. During the second attack her blood-pressure rose to 220/140 mm. Hg.

The patient made steady and fairly rapid progress. Four weeks after the start of her illness the bulbar signs had disappeared, and by the fifth week the external ocular movements were normal and she had no nystagmus or circumoral parasthesiæ; she could sit up and turn about in bed unaided. By the ninth week she could walk with assistance, and by the eleventh the sensory signs had cleared. The hypertension gradually subsided during convalescence, the blood-pressure eventually settling at 120/80 mm. Hg. The E.E.G. also reverted to normal. Three months after the onset of her illness the patient could walk unaided and normal menstruation had returned.

The only residual disability is moderate weakness of both anterior tibial muscles, causing partial bilateral foot-drop. Improvement is continuing.

Comment

Clinically this case resembled previously reported cases of mumps polyneuritis (Miller et al. 1956) in the severity of the tetraplegia, its association with lower-cranial-nerve palsies, and the considerable albuminocytological dissociation of the C.S.F. The present case differed from the hitherto reported cases in the severity of sensory loss (rather an inconstant feature in previous cases and, when present, rarely extreme) and in the development of meningoencephalitis (nuchal rigidity, fits, and stupor), *subsequent to* the development of polyneuritis. Of the various parainfectious neurological syndromes, polyneuritis has the longest latent period. It is hardly ever followed by meningoencephalitis.

The hypertension was assumed to be of "central" origin in view of its acute onset and eventual complete subsidence, the absence of any alternative cause, and the known association of hypertension with certain inflammatory disorders involving the brain-stem.

The diagnosis of mumps in non-parotitic cases must of necessity rest on laboratory evidence. Isolation of the virus from the C.S.F. has proved feasible in a large proportion of cases of lymphocytic meningitis due to mumps (Kilham 1949, Kilham et al. 1949), but in patients presenting with other neurological disorders serological evidence has to be relied on. In our patient the serum showed increases of complement-fixing-antibody titre equal to or exceeding the fourfold increase suggested by Kilham (1949), and subsequently accepted by others (Feller and Jordan 1950, Adair et al. 1953, Horstmann 1956, Wolman 1957), as diagnostic.

We wish to thank Mr. T. L. T. Lewis, who referred the patient to us, and Dr. C. E. D. Taylor, for his help with the serological investigations.

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TREATMENT OF UNUSUAL CASE OF ANURIA

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THIS case of acute renal failure, treated by the conservative method of Borst (1948) and Bull et al. (1949), presented unexpected and interesting features.

Case-record

An unmarried woman, aged 48, had a rigor, followed by dysuria, frequency, and nocturia, ten days before admission on Oct. 29, 1958. Nausea and retching began four days later. She had occasionally had frequency and dysuria, for one to two days, throughout several years. Since 1952 she had been incapacitated by rheumatoid arthritis, and, because of this, had taken 200 mg. phenylbutazone daily for five weeks prior to admission. She was in hospital in 1952, because of the arthritis, and in 1955, suffering from " pneumonia ".

She had typical rheumatoid deformities. Her temperature was 100·6°F. There was no other abnormality on clinical examination, and her tongue was moist. The urine contained many pus cells and fine granular casts, and culture showed *Escherichia coli*. Albuminuria (3/4 part Esbach) and ketonuria were found, and the reaction to Benedict's solution was green. The hæmoglobin level was 12 g. per 100 ml.; white blood-cells 10,600 per c.mm.; erythrocyte-sedimentation rate 96 mm. in the first hour (Westergren); blood-urea 41 mg. per 100 ml.; serum-proteins normal. The lupus-erythematosus-cell test, Wasserman reaction, and gonococcal fixation test were negative, and the Rose-Waaler test was strongly positive. The fasting blood-sugar was 93 mg. per 100 ml. X-ray of chest and electrocardiogram were normal.

Treatment and Course

Acute pyelonephritis was diagnosed, and treatment started with alkalis, fluids, light diet, and ' Sulphatriad ' 1 g. t.i.d. Intake and output were satisfactory, though the patient vomited small quantities of fluid. On the fourth day she complained of central abdominal colic, but no abnormality was detected. Urinary output on the sixth day was only 235 ml. Sulphatriad was discontinued, and four pints of 5% glucose given intravenously without effect. The patient was anuric for eleven days. She was placed on the regime outlined by Bull (1958). An intragastric drip was maintained for twenty-two days, during which 250–300 g. glucose was given daily. Vomiting was persistent, but the fluid lost was easily replaced. Water and electrolytes lost through diarrhœa were replaced by equivalent fluids. Antibiotics and vitamins were given orally. The grave illness ran a typical course, with the highest blood-urea level—310 mg. per 100 ml.—on the eighteenth day. The serum-potassium level was high at first, but with the high carbohydrate intake, and two injections of isobutyrate crystals of testosterone (' Perandren ' 50 mg.), it remained just within normal limits until diuresis began, when it fell to dangerously low levels which proved difficult to correct with intensive oral potassium.

On the fourth day of anuria cystoscopy was performed. The bladder was healthy, and the ureteric orifices were normal. The ureteric catheter was held up at 1 cm. on the left side. Pyelogram of the right kidney was normal. The few drops of urine in the bladder contained many pus cells, a very occasional red blood-cell, and, on culture scanty proteus and enterococci. No crystals were seen. Serum-sulphonamide was 4·2 mg. per 100 ml.

Two days later the patient was very ill, and rapidly became dehydrated and confused. Her condition resembled that of a diabetic almost in coma. Blood-sugar at 3 P.M. was 760 mg. per 100 ml. Despite 24 units of soluble insulin, and oral saline (one-third physiological), it was 900 mg. by 10.30 P.M. 60 units of soluble insulin brought the level down gradually to 100 mg. at 9 A.M. Throughout the night the patient was paranoid, with Kussmaul respirations and rhonchi at the lung bases. The danger of hyperglycæmia was now appreciated, and blood-sugar levels were controlled by insulin (see figure). With this, and control of infection, the patient slowly recovered. She developed a generalised drug rash after intramuscular tetracycline, and again after intramuscular penicillin.

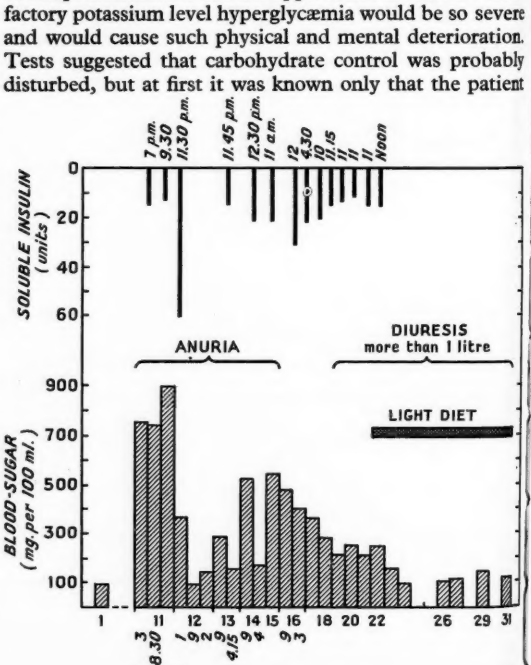
The first urine passed after eleven days, and blood taken at the same time gave blank values for phenylbutazone. This was eighteen days after the last dose.

On the thirtieth day of illness liver-function tests were found to be abnormal: thymol flocculation + + +; cephalin-cholesterol + + + +; prothrombin-time 27 sec.; serum-albumin 3·2 g., globulin 3·2 g., per 100 ml. These slowly became normal. Two oral, and one intravenous, glucose-tolerance tests gave diabetic curves, and also suggested abnormal leakage of glucose in the urine. Urea-clearance was 29%, and maximum concentration of urine 1006. Seven months later an oral glucose-tolerance test was normal, concentration reached 1012, and urea-clearance was 45%.

The case-notes for 1955 showed the the patient's previous illness had been acute pyelonephritis, with *Esch. coli* infection, following phenylbutazone for several weeks. Treatment was with sulphatriad and alkalis, but, because of vomiting, finally with tetracycline. The urinary output was low on two occasions (7 oz., 14 oz.) at times when intake was low.

Discussion

This patient's history emphasises two points in the conservative treatment of acute renal failure: (1) blood-sugar estimations are essential, and (2) insulin control of hyperglycæmia will probably be necessary. Insulin is generally administered, primarily in order to promote the formation of glycogen and a potassium-glycogen cellular complex, to prevent a dangerously high serum-potassium level (Fenn 1940, Bywaters and Joekes 1948, Bull et al. 1953). De Wardener (1958) refers to this, but not to the necessity for insulin control to prevent hyperglycæmia. In the present case it was not appreciated that with a satisfactory potassium level hyperglycæmia would be so severe and would cause such physical and mental deterioration. Tests suggested that carbohydrate control was probably disturbed, but at first it was known only that the patient



Blood-sugar levels and insulin dosage.

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had a normal fasting blood-sugar. Evans et al. (1953) have pointed out the importance of routine blood-sugar estimations, since high levels develop in many cases. Rennie (1958) recommends that the blood-sugar be estimated every third day, and that 10 units of soluble insulin be given three times each day if the level much exceeds 250 mg. per 100 ml.

The cause of acute renal failure in this patient has not been accurately determined. She had an acute urinary infection and probably chronic renal infection, on admission. On ureteric catheterisation, however, there was no abnormality and no crystals were found. This suggested that the sulphonamide was not responsible, and the blood-sulphonamide level was low. Tests suggested hepatocellular damage, and an upset of carbohydrate metabolism, which, in association with abdominal pain, might have been due to pancreatitis or hepatitis. The patient had received 200 mg. phenylbutazone daily for five weeks, and had had a remarkably similar illness in 1955 following the same drug. Twice while in hospital she exhibited hypersensitivity to drugs. Her latest illness was probably due to idiosyncrasy to this drug associated with already poor renal function. During convalescence she appeared to have diminution in function of the proximal convoluted tubule, shown by daily glycosuria. This is a rare sequel to acute renal failure (Bull et al. 1950), but could be a nephrotoxic effect.

Toxicity of phenylbutazone can develop after small doses (Steel and Moffatt 1954, Wood 1954, Fraser 1955). In the case reported by Johnson and Larkin (1954) the patient had contracted kidneys and poor renal function, which they suggested should preclude the use of the drug. Toxic effects may occur after the drug has been stopped. Blood-levels fall over seven to fourteen days, and blank values are found after fourteen days (Bruck et al. 1954, Huffman et al. 1954, Wood 1954). Phenylbutazone has been reported as causing widespread visceral damage, including hepatitis, pancreatitis, and renal tubular damage and has caused acute renal failure (Bourne 1953, Freeland et al. 1953, Stifel and Bunheimer 1953, Bruck et al. 1954, Engleman et al. 1954, O'Brien and Storey 1954, Fraser 1955, MacCarthy and Jackson 1955). The most interesting parallel is with the case reported by Nassim and Pilkington in 1954, where the urine contained albumin, bile, urobilinogen, and granular casts a few days after phenylbutazone was discontinued.

Ten days later there was pronounced glycosuria and a diabetic glucose-tolerance curve, and the patient required insulin for ten days. Serum-amylase was normal, but liver-function tests were abnormal, and liver biopsy showed changes thought to be due to toxic damage. It was several months before liver-function tests and glucose-tolerance became completely normal. No previous case had shown transient hyperglycæmia responding to insulin. The involvement of so many viscera was thought to suggest a hypersensitivity reaction.

Summary

A case of acute renal failure, treated by conservative methods, is described.

Blood-sugar estimation is important in such cases, and hyperglycæmia must be controlled by insulin.

In the present case the cause was apparently hypersensitivity to phenylbutazone.

I thank all those in the unit and the Western Infirmary who worked so hard for this patient, and in particular Dr. James Reid for his advice and encouragement.

References at foot of next column

FIBROCYSTIC DISEASE OF THE PANCREAS IN A MAN AGED 46

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IN recent years patients with fibrocystic disease of the pancreas have been observed to reach greater age in a better clinical state than previously. Most of this improvement has been attributed to the use of antibiotics and other measures in controlling the pulmonary infection which so frequently causes death. But an increasing number of cases has been diagnosed in later childhood, and there have been predictions that cases would be discovered in adult life, especially where the full established clinical picture had not been present from birth (Andersen 1958). Andersen (1958) mentions a patient aged 35 years who was found at necropsy to have certain features suggestive of this condition, but she said that the diagnosis was far from established in that instance.

In the case described here a man aged 46 years presented with a combination of chronic pulmonary suppuration and pancreatic insufficiency, and he is thought to have fibrocystic disease of the pancreas.

Case-record

A shopkeeper, aged 44, was referred to one of us (B. L. M.) in April, 1958, with a history of cough and sputum for as long as he could remember, and certainly since the age of $2^1/_2$ years. His sputum, which had always been yellow, had in recent years increased in amount to 2 oz. daily. He recollected wheezing in childhood, but this was abolished by coughing up his sputum. Each morning he spent a few minutes "clearing" his chest. Effort tolerance had been somewhat impaired for years, although he could still climb three flights of stairs quite briskly. There were days when he was more wheezy than usual, but the dyspnœa was constant. Purulent nasal discharge had been present since childhood. His nose was usually blocked and his sense of smell was poor. Colds were common. He had had pneumonia at the ages of $2^1/_2$, 7, 10, 29, and 34 years, and had been severely ill on the last two occasions.

His mother did not consider him to be strong as a child, and he had always looked after himself carefully. His sisters were of normal height, but he was usually the shortest in his class. His appetite was always large, but for some years it had been voracious. He passed two motions daily during childhood, and

DR. GIBSON: REFERENCES

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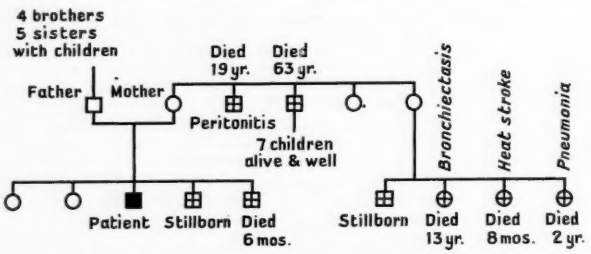

Fig. 1—Family tree, showing evidence of deaths in childhood.

had noted fatty oozing from the anus since the age of 20. Severe diarrhœa started after his attack of pneumonia at the age of 29, and has continued since; there have been five to eight motions daily, orange and often fluid.

Vision had been poor for two years and had been improved by local injections of cortisone. He had been married for many years but had had no children. Sterility had been investigated seventeen years previously; his wife was then said to be normal. He was stated to have had azoospermia. Testicular biopsy was normal.

Family History

The family history (fig. 1) was of some interest. One brother was stillborn and the other died at the age of 6 months; for some time before death this child had opisthotonus, the cause of which was not ascertained. Two sisters were alive and well. One of his mother's sisters had borne 9 children, 5 of whom were alive and well; but of the remainder 1 had been stillborn, and 3 daughters had died early in life. 1 of these had proven bronchiectasis and was known to have been puny; she died unexpectedly at the age of 13 years during a general anæsthetic. Another child died at the age of 8 months, probably of heat stroke. The 3rd child died at the age of 2 years of pneumonia, but no further information is available about her.

Physical Examination

The patient was short, slight, and wheezy. Bilateral submandibular salivary-gland enlargement was apparent. There was no finger-clubbing. The anteroposterior diameter of the chest was increased, movement was poor, and cardiac and hepatic dullness were diminished; the percussion note was generally hyperresonant; many rhonchi were audible, and there were fine crepitations posteriorly up to the level of the scapular angles; air entry was quite good. Examination of the ocular fundi showed bilateral choroiditis with vitreous opacities. The liver and spleen were not palpable.

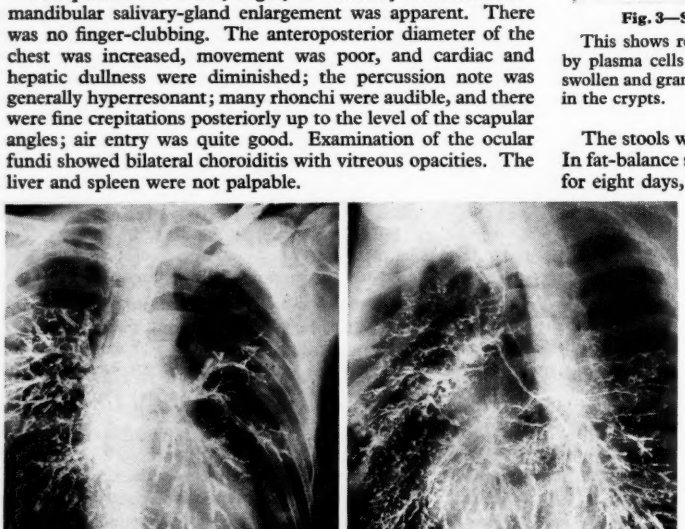

Fig. 2—(a) Anteroposterior and (b) right anterior oblique radiographs of bronchograms made in 1948.

These show "bangling" and dilatation in the left apicoposterior bronchus, poor filling and irregularity of calibre in many of the branches of the left lower lobe, and dilatation and irregularity of branches of the right middle lobe and right posterior basal segment.

Investigations

X-ray examination of the chest showed generalised fine fibrosis, more pronounced in the lower zones. Bronchography had been carried out in 1948 (fig. 2). Widely distributed "bronchitic" change was apparent comprising sparse branching, irregularity of bronchial calibre, and "bangling"; but, although present in most lobes, it was not gross. Several small bronchi were dilated, and here peripheral puddles of contrast medium were visible suggesting slight bronchiectasis. Respiratory function tests showed the typical pattern of a moderately severe obstructive defect. The tests were considered compatible with chronic bronchitis with or without emphysema. The ventilatory response to exercise was rather high. The ventilatory tests conformed to the pattern found in children with fibrocystic disease of the pancreas with moderate pulmonary involvement (Gandevia and Anderson 1960). Sputum culture did not reveal any pathogens.

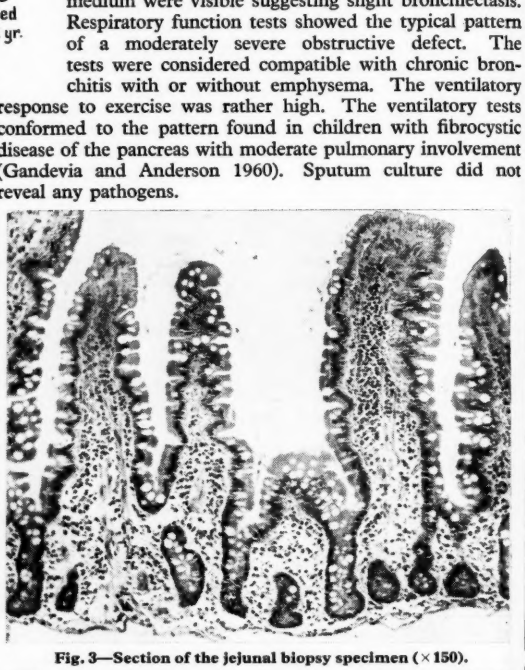

Fig. 3—Section of the jejunal biopsy specimen (×150).

This shows relatively normal villous form, with some infiltration by plasma cells and lymphocytes. Goblet cells are numerous and swollen and granular eosinophilic-staining mucous material is present in the crypts.

The stools were bulky and greasy and contained oil droplets. In fat-balance studies the patient had a daily fat intake of 190 g. for eight days, and during the second four days of this period fat output in the stools averaged 140 g. daily. Duodenal intubation yielded clear viscid orange fluid of pH 7·0–8·6. Three specimens contained no trypsin, amylase, or lipase. Aspirate was again obtained after giving 1 unit of secretin per kg. body-weight by intravenous injection. In the forty minutes preceding the injection 14·0 ml. of fluid was obtained containing 0·22 millimol of bicarbonate (normally 90–199 ml. containing 10·7–17·75 millimols). In the forty minutes following secretin the output rose to only 26·5 ml. containing 1·03 millimols of bicarbonate. The pH of two specimens obtained before secretin was 7·5 and 7·8; these contained 0·8 and 0·5 unit of lipase respectively, but neither trypsin nor amylase. After secretin the specimens were of pH 8·0 and 8·2; they contained 0·8 and 0·7 unit of lipase, but again neither trypsin nor amylase. X-ray of the pancreas did not reveal any calcification. Serum-cholesterol was low (108 mg. per 100 ml.). Xylose absorption test and glucose-tolerance curve did not reveal malabsorption.

Liver-function tests, including estimations

of serum-bilirubin, thymol turbidity, thymol flocculation, zinc-sulphate turbidity, alkaline phosphate, serum albumin and globulin, and gamma-globulin, were normal. Hæmatological examination was normal.

A mecholyl sweat test was carried out, using the technique of Anderson and Freeman (1958). The sodium and chloride concentrations of the sweat obtained were respectively 85 and 71 mEq. per litre.

Small-bowel suction biopsy was carried out by the method of Shiner (1957). The specimen (fig. 3) showed a normal villous pattern, but an inflammatory infiltrate mainly of plasma cells was present through the lamina propria. Swollen goblet cells were extremely numerous, and some of the crypts were filled with granular eosinophilic staining material. The right submandibular salivary gland was removed for biopsy. Section of the somewhat enlarged gland was within normal limits.

Spermatazoa were absent from specimens of seminal fluid. Biochemical studies of the seminal fluid suggested normal prostatic function but very little seminal vesicular function.

Treatment

An attempt was made to control bronchial infection with long-term broad-spectrum antibiotics, and later pancreatic extract was administered. The patient was started on tetracycline 250 mg. six-hourly by mouth. He has since produced only 1–2 drachms of mucopurulent sputum daily; cough is much less; effort tolerance has improved; nasal discharge has ceased; and vision has improved. He was then given ' Pancrex 15 ', a concentrated pancreatic extract, in a dosage of 0·5 g. t.d.s. with meals. Since then he has passed only one or two well-formed stools daily and there is no longer any oily discharge. His appetite is much reduced, but despite this he has gained several pounds in weight.

Discussion

In this case a diagnosis of fibrocystic disease of the pancreas is worth considering because of the association of pancreatic achylia with widespread bronchial disease and the suggestive family history. Investigation has done nothing to disprove the diagnosis. The evidence from the gastrointestinal studies points strongly towards the steatorrhœa being of pancreatic origin. Small-bowel biopsy did not show the mucosal changes seen in idiopathic steatorrhœa, but the appearance of mucus-secreting cells and the mucous were similar to those in fibrocystic disease of the pancreas. In this respect, the section (fig. 3) shows a remarkable similarity to those of small and large intestine demonstrated by Bodian (1952) in his monograph on this disease.

It is difficult to suggest a reasonable differential diagnosis, unless the conditions are felt to be unrelated. Pancreatic achylia has a number of causes, most of which are unlikely in this patient. Mumps is a rare cause of such selective pancreatic damage. Chronic pancreatitis is very unlikely in view of the absence of a history of pain, of diabetes, and of calcification on X-ray.

The pulmonary changes are compatible with widespread damage from several causes, but they are not typical of ordinary bronchiectasis in that bronchial dilatation is slight and of unusual distribution. In children who have died of fibrocystic disease of the pancreas emphysema is usually much more severe than in the present case. However, cases of fibrocystic disease with less severe pulmonary involvement are seen, and in these emphysema is not so prominent. Respiratory function tests in the present case gave similar results to those in children with fibrocystic disease of the pancreas, rather than in adults with emphysema.

A good deal of diagnostic reliance is placed on the sweat test in children with fibrocystic disease of the pancreas. The figures obtained in the present case are outside the normal range in healthy children (i.e., above 70 mEq. per litre), but are within the upper limit of values found in a series of normal adults by Anderson and Freeman (1958). The results of this test are as yet difficult to interpret in adults owing to the uncertainty of the range of adult sweat-electrolyte levels.

It had been hoped that the resected submandibular salivary gland would show the changes occasionally found in children with the syndrome, but apart from its large size there was nothing unusual about the gland. In the great majority of childhood cases, the salivary glands are also normal.

Sterility investigations suggest seminal vesicular deficiency, and it is tempting to regard this as possibly associated in some way with fibrocystic disease. There is no reported case of parenthood in a proven case of this condition, and it will be of interest to learn whether sterility is usual as more patients reach adulthood.

There appears to be no documented case of fibrocystic disease of the pancreas of comparable age to that of the present case. Andersen (1958) rejects several on various grounds, but states that she expects genuine older cases to be found. We feel that this case reasonably fulfils the required criteria.

Summary

A middle-aged man with features of long-standing bronchial infection was found to have chronic diarrhœa.

Investigation disclosed that the chest infection was of unusual type, with widespread bronchial damage. The diarrhœa was due to pancreatic achylia. Many swollen mucus-secreting cells were present in a biopsy specimen of the small-intestinal mucosa.

There was a family history of deaths in childhood in brothers and first cousins, in part due to disease of the chest.

The patient is believed to have fibrocystic disease of the pancreas, and if the diagnosis is correct this is the oldest reported case.

Many people have given assistance, particularly with the investigations, and in this respect we wish to thank the staffs of the clinical research units of both the Royal Children's Hospital and the Royal Melbourne Hospital. Dr. Ian Wood performed the intestinal biopsy, Dr. Bryan Gandevia the respiratory function tests, and Dr. Eric McKay the seminal investigations.

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". . . It is necessary to avoid the error of supposing that tropical medicine is an entity separate and distinct from medicine in the other regions of the world. It is certainly true that there exist within the tropics diseases of great prevalence and importance that are not found in cooler climates, but these diseases are found superimposed upon a basic disease pattern which is not dissimilar to that seen in advanced Western countries. . . . The frontiers of tropical medicine today are set so wide that the doctor is thankful to join forces with the biochemist, the geneticist, the sociologist, the educationist, the agronomist and many other specialists; which is precisely the case with medicine in other climates; and it is not so long ago that what is (significantly) never called ' temperate medicine ' had to cope with health problems on a scale almost as vast as that which confronts us in tropical countries."—Dr. IAN MCGREGOR, *Listener*, Jan. 7, 1960, p. 15.

Preliminary Communication

RELATION OF FREE CORTICOSTEROIDS IN URINE TO STEROID DOSAGE

IN clinical practice the urinary excretion of 17-hydroxy-corticosteroids—i.e., 17(OH)CS—is a measure of whether a patient has excess hydrocortisone (cortisol) or is in need of it. Experience has shown that excess is accompanied by above-average excretion, and deficiency by below-average excretion. Recent studies of the protein binding of hydrocortisone show that the small diffusible fraction determines the clinical effectiveness of hydrocortisone, and that the diffusible fraction does not vary directly with the protein-bound fraction as the blood-level rises.[1] This being so, assays of plasma hydrocortisone are not an accurate guide to the effective concentration of hydrocortisone, and it is not likely that the urinary excretion of 17(OH)CS is an accurate guide either.

The excretion of free unmetabolised hydrocortisone in the urine may provide a measure of the effective (diffusible) fraction in the blood.[2] Because of the recent protein-binding studies this suggestion can be tested, since one can predict from them how much hydrocortisone should appear in the urine if the excretion varies with the level of diffusible hydrocortisone.

METHOD

To induce a steadily rising blood-level a normal subject took hydrocortisone daily in divided doses, increasing the dose by 20 mg. every two days. Twenty-four-hour specimens were collected under toluene, and the excretion of hydrocortisone, cortisone, and total 17(OH)CS was measured.

Hydrocortisone and cortisone were measured by the methods of Bush,[3] with minor modifications suggested to us by Dr. Bush. Total 17(OH)CS was measured by the method of Appleby et al.[4]

RESULTS

Fig. 1 shows the mean excretion of hydrocortisone, in micrammes, for each two-day period, and of total 17(OH)CS in milligrammes. Except for the last three days' hydrocortisone excretion, the pairs of assays were too close to be depicted separately. The rate of increase of hydrocortisone excretion is what could be predicted from the protein-binding studies.

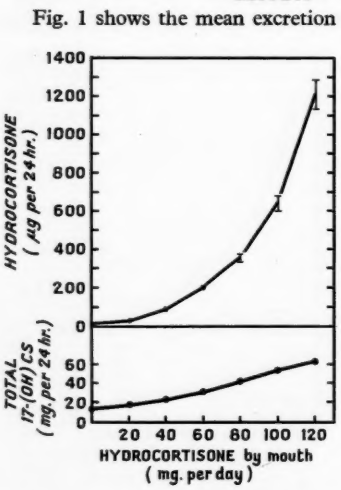

Fig. 1—Increase in the absolute and relative excretion of hydrocortisone and total 17(OH)CS at successively higher doses of hydrocortisone.

Fig. 2, the curve of the excretion of hydrocortisone plus cortisone, is included because the biological significance of free cortisone in the blood is unknown.

DISCUSSION

To know just how accurately the urinary free hydrocortisone reflects the diffusible level in the blood we must await more complex studies in which this blood-level is measured over the same period as the urinary levels. Nevertheless our findings, which reasonably fulfil prediction, do show great disparity between the estimates from the excretion of free hydrocortisone and those from the excretion of 17(OH)CS metabolites. They are consistent with the very considerable evidence that steroids act as catalysts, and that their metabolites result largely from the disposal mechanisms of the liver. The rapid rise in effective steroid level as doses in the physiological range are exceeded is consistent with the clinical finding that long-term side-effects increase rapidly with small increments of dosage (e.g., prednisolone 7·5→10→12·5 mg.).

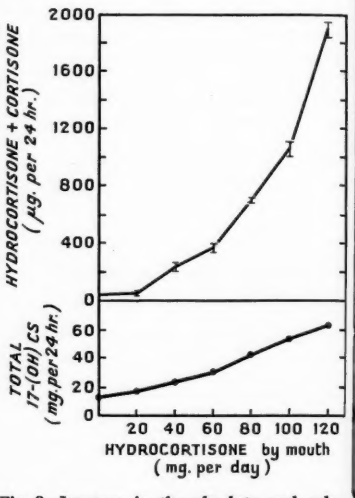

Fig. 2—Increase in the absolute and relative excretion of hydrocortisone plus cortisone, and of total 17(OH)CS, at successively higher doses of hydrocortisone.

An obvious criticism of urinary assays is that the findings may be upset by tubular reabsorption or excretion. Since our study Schedl et al.[5] have reported that 80–90% of filtered hydrocortisone is reabsorbed, and that glomerular filtration-rate and urine volume seem to have little effect. This is reassuring. The absolute figures given above are consistent with 80–90% reabsorption. So little hydrocortisone is lost in the free form that, from teleological reasoning, one would not expect to find a purposeful selective reabsorption of hydrocortisone.

We conclude that the estimation of free hydrocortisone in urine is a promising means of estimating the effective level of the hormone in the blood, and that it may well prove far more revealing than the measurement of urinary hydrocortisone metabolites.

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"... although a scientist may accumulate knowledge, wisdom is as difficult for him to acquire as for anyone else."
—Dr. MAGNUS PYKE, *The Listener*, Jan. 21, 1960, p. 125.

New Inventions

A BAG FOR MEASURING RESPIRATORY VOLUMES

IT is often desirable to measure the vital capacity or minute volume of a patient with respiratory insufficiency; but most methods are clumsy, inaccurate, expensive, or not available at the bedside. We have used a small calibrated hexagonal plastic bag (fig. 1), which is made by welding together two sheets of polyvinyl chloride (P.V.C.) $^{10}/_{1000}$ in. (0·25 mm.) thick, and which has a P.V.C. inlet tube of $^{1}/_{2}$ in. (1·25 cm.) bore. The obtuse angles make for easy and complete emptying, since air cannot pocket. The design incorporates a wooden rod of 1 in. (2·5 cm.) diameter at the lower end. When this is rolled up the long axis, the bag becomes wrapped round it, and is therefore emptied completely. A small rubber band can conveniently keep the bag rolled and ready for use. When the outlet tube is occluded, the wooden rod can only be rolled partly up the length of the bag. The distance from the rod to the neck, as measured by the scale on the bag, is an accurate function of the volume of gas contained (fig. 2).

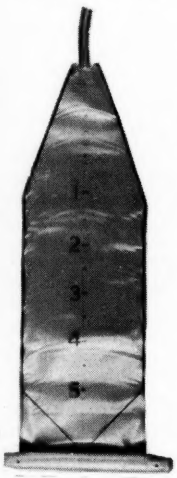

Fig. 1—The bag. The air compartment is outlined in black, and intermediate points on the litre scale have been omitted.

We have measured various respiratory-air volumes, and since, for example, the minute volume of expired gas from a respirator may be many times greater than the vital capacity of a severely disabled patient, we have used two bags of different sizes for different purposes. The larger, which can be used for smaller volumes if accuracy is not of first importance, is 12 in. (30 cm.) wide and the smaller is 8 in. (20 cm.) wide. A convenient total length for each is about 24 in. (60 cm.), including tapers of 8 in. (20 cm.) at the inlet end and 4 in. (10 cm.) at the other.

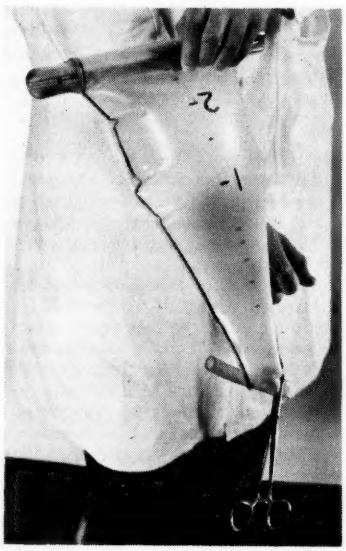

Fig. 2—Measurement of a volume of about 2·6 litres. (Scale simplified for clarity.)

THE BAG IN USE

The basic principle is that the observer should roll up the bag until the part containing gas is fairly tense. We have found it most satisfactory first to roll the bag with both hands, and then to hold the rod in one hand and rest the bag on the other forearm, rolling until the tension feels correct (fig. 2). While maintaining this degree of tension, which is arbitrary, the position of the rod on the scale should be read.

Errors may arise from variations of pressure on the gas, from various degrees of indentation of the bag, and from simple variations in reading the scale. But a series of suitably designed experiments has shown that the results are consistent for any one observer, and that the pressure to which he rolls the bag does not depend on practice. The method described above of handling the bag and reading the scale can be repeated reasonably accurately (table I). Most observations by one observer fall within the range $\pm 2\%$ of his mean estimate. The results obtained by different observers, however, show regular differences. One observer may consistently produce results whose mean is $\pm 3\%$ from the correct value, but such a large error is uncommon. Differences between the results obtained by various observers are largely due to differences in the pressure which they use and the compliance of the bag system. Hence if a particular observer calibrates a bag to his own method of handling, the results show a standard deviation from the mean of less than 2%, for volumes greater than 2 litres (table II).

TABLE I—TWO SERIES OF ESTIMATIONS OF GAS-VOLUME, USING THE LARGER BAG, MADE BY FOUR OBSERVERS AT 4 WEEKS' INTERVAL

Observer	*Series I* 10 observations: correct value 8·47 l.		*Series II* 5 observations 4 weeks later: correct value 8·67 l.	
	% error of mean	% range of errors	% error of mean	% range of errors
A	−0·83	−2·01/+0·35	+1·50	+0·3/+2·7
B	−3·30	−4·36/−0·83	−1·73	−2·0/−0·8
C	+0·12	−0·83/+1·53	−1·96	−3·1/−0·8
D	−3·18	−5·56/−0·83	−3·57	−4·3/−3·1

The observers had not used the method before the first observations nor during the 4 weeks' interval.

TABLE II—ESTIMATIONS MADE BY ONE OBSERVER USING THE LARGER BAG CALIBRATED TO HIS OWN TECHNIQUE

True value (l.)	8·47	1·86
Mean of 30 estimates	8·42	1·83
% error of mean	−0·59	−1·61
% range of errors	−2·01/+3·90	−1·31/+2·69
S.D. of 30 estimates about mean value (%)	1·33	1·64

The above results apply to the larger bag. The smaller one can be used with similar accuracy to measure smaller volumes. The shape of the taper is such that the difference between 200 ml. and 300 ml. of gas is equivalent to a distance of 1 in. on the scale.

The most satisfactory method of estimating minute volume is to collect and measure the volume of gas breathed in a number of complete respiratory cycles occupying about 60 sec., timing the period accurately (Cooper 1959).[1] One can conveniently draw on the bag a nomogram from which the minute volume can be read without calculation, since, when time is represented transversely (along the axis of the rod), the rod acts as the cursor on the nomogram.

These bags can be cleaned simply by rinsing, but at times they may be contaminated by viscid sputum. Satisfactory readings have been obtained with a bag in which the wooden rod is split in its long axis and held together by countersunk nuts and bolts. The bottom of the bag is not sealed. Thus when the rod is taken apart the bag can be opened for cleaning.

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1. Cooper, E. A. *Anæsthesia*, 1959, **14**, 373.

Reviews of Books

The Royal College of Surgeons of England—A History

SIR ZACHARY COPE, F.R.C.S. London: Anthony Blond. 1960. Pp. 360. 63*s*.

THE pillars of the Royal College of Surgeons have a serenity about them which makes it easy for the visitor to Lincoln's Inn Fields to realise that they have stood thus for well over a hundred years: and that behind them lie the headquarters of a body whose origin can be traced back for at least four times as long. He may find it more difficult to credit that, in their day, these buildings have reverberated with the efforts of the Bow Street runners to separate their dissenting occupants: or that, at another time, these doors were barred, by the council of the college, against its own members.

The story behind these affairs—and many more memorable and creditable activities—is here related by Sir Zachary Cope, already celebrated as surgeon, historian, and writer. For this latest work he has a particular qualification, in that for nine years he was a member of the council of the college. The detailed study he has now given of its evolution will be appreciated by historians everywhere—because, despite the college's venerable age and complete records, no such account has previously been published.

But Sir Zachary's book is likely to find its keenest readers amongst his colleagues, the fellows and members of the college, and they will learn from it much that is likely to be new to them: that when a council meeting ends, each of those who have been present throughout receive a guinea for their pains; that the Speaker of the House of Commons and the First Lord of the Admiralty are both trustees of the Hunterian Collection; and that a former president of the college once petitioned Parliament not to grant a new charter to it.

Even those who have failed in their aspiration to fellowship or membership will derive some pleasure from the book, and they will certainly sympathise with the disappointed Conjoint candidate who, in July, 1920, greeted the news of his rejection by discharging a revolver six times in the Inner Hall, and threatening a college servant. And any who have been tempted to condemn the court of examiners as unreasonable should note that this same candidate was given permission to present himself again, only a year later.

Coronary Heart Disease

J. W. GOFMAN, M.D., PH.D., professor of medical physics, University of California. Oxford: Blackwell Scientific Publications. 1959. Pp. 353. 60*s*.

THE author has made a distinguished contribution to the study of ischæmic heart-disease by showing that this disorder is associated with an altered physical condition of the lipids in the blood. Measurements with the ultracentrifuge show increased quantities in plasma of those lipoproteins which are of low density and so can be separated and measured in a high gravitational field. This change is clearly connected with the better-known rise in plasma-cholesterol also associated with the disorder. From measurements of the concentrations of various components of the lipoproteins, Professor Gofman calculates an atherogenic index which he claims can be used to measure the risk of an individual to future clinical attacks of ischæmic heart-disease. For some years, however, there have been claims that the atherogenic index is, at the best, an expensive substitute for a measurement of the plasma-cholesterol. The evidence presented in this book is not such as to make many of the author's opponents change their minds on this point. Few hospital laboratories in Britain possess an ultracentrifuge and we do not know of any convincing evidence that the need for one is strong.

Much of this book is taken up with discussions of the relations of high blood-pressure, heredity, age, sex, overweight, diet, cigarette smoking, diabetes, and thyroid disease to ischæmic heart-disease. These epidemiological studies are not always easy to follow: on two occasions the author allows himself to run for over four pages without a fresh paragraph.

Professor Gofman is an expert physicist, and there are important biophysical aspects of ischæmic heart-disease; but this book is in some ways disappointing, for one would like to know more about these aspects and less about his disagreements with the biochemists, who after all are studying the same phenomena though from a different angle.

A Guide-Book to Biochemistry

KENNETH HARRISON, lecturer in biochemistry, University of Cambridge. London: Cambridge University Press. 1959. Pp. 150. 17*s*. 6*d*. (10*s*. 6*d*. paper-bound.)

THIS book is intended to present the bare bones of biochemistry. It aims at being useful in schools for telling pupils what biochemistry is about, and to help them to decide whether to take it as one of their university subjects. It also hopes to provide an introduction for specialists in other branches of science, and for students beginning to study biochemistry.

Advantage is taken of two devices: a kind of shorthand which abbreviates elaborate chemical structures in capital letters, such as A.T.P. and D.P.N.; and " flow sheets ", whereby the pattern of complicated reactions is demonstrated by following carbon, phosphate, or chemical names through a sequence of changes without constant attention to the intricacies of chemical changes. An appendix gives the formulæ of fourteen " carrier " molecules, such as A.M.P., A.D.P., D.P.N., T.P.N., and U.D.P.G., and discusses them in detail (adenosine monophosphate, adenosine diphosphate, diphosphopyridine nucleotide, triphosphopyridine nucleotide, uridine diphosphate glucose).

Not all of the chapters, which cover energy, enzymes, oxidation, photosynthesis, carbohydrates, fat, protein, and the control of their metabolism, will be equally understood by schoolboys and non-biochemical scientists or doctors, but on the whole the author's aim is achieved. In a future edition the statement that mitochondria contain the enzymes synthesising fatty acids should be corrected.

Transplantation of Tissues

Vol. 2. Editor: LYNDON A. PEER, M.D., clinical and research director, Rehabilitation Center for Plastic and Reconstructive Surgery, St. Barnabas Medical Center, Newark, N.J. Baltimore: Williams Wilkins Co. London: Baillière, Tindall & Cox. 1959. Pp. 690. 160*s*.

FOUR years have passed since volume 1 of this large work appeared, and they have been fruitful ones for its subject. A growing literature testifies to this, and one of the assets of the new volume is its comprehensive review of both new and established work. It covers a much wider field than its predecessor. The editor, Dr. Peer (he was the author of the first volume), has twelve other contributors. P. B. Medawar on the zoological laws of transplantation, D. M. Hume on renal grafts, and Ramon Castroviejo on the cornea speak with the authority one would expect. Blair O. Rogers in an interesting section on skin draws from history as well as genetics and immunology. Dr. Peer's own article is on fat grafts, and it will surprise most readers to find 80 pages devoted to this topic, particularly when 24 were considered sufficient for the cornea. Deterling has given as comprehensive a statement on blood-vessel grafts as could be wished for: it covers the entire development of this new adjunct to vascular surgery, from the work of Carrel to the uneasy state which now prevails because of the apparent succession of cloth prostheses to the place of choice in preference to homografts. Equally valuable are the sections devoted to nerve (the late Sterling Bunnell), endocrine tissue P. L. Krohn), and tissue culture (Mary Parshley).

This book, filled with countless carefully presented observations and the mature reflections of experts, makes it plain that transplantation still awaits its Fleming, its Banting and Best: this " new dimension of accomplishment ", as Medawar puts it, is the most important subject facing surgical science today. This book will have an important function in admitting more interested readers to a difficult but exciting realm of knowledge, and the guidance it gives may well add further impetus to the search for understanding.

THE LANCET
LONDON 13 FEBRUARY 1960

Acute Tubular Necrosis

ACUTE tubular necrosis is the commonest cause of acute oliguric renal failure. If the patient does not die in the first few weeks of the illness, virtually complete recovery of renal function ensues,[1–3] and susceptibility to further kidney damage is apparently not increased. The management of this condition has greatly improved in the post-war years with the introduction of conservative measures to reduce the rate of clinical deterioration [4 5] and of hæmodialysis by the artificial kidney [6]; and a few years ago the results of treatment were giving rise to optimism. Thus STRAUSS and RAISZ [7] wrote in 1955: "The mortality in acute tubular necrosis itself can be reduced by a combination of physiologic measures and external dialysis to nearly zero." About this time, however, reports of treatment of acute tubular necrosis in wounded soldiers in Korea [8 9] gave a less satisfactory picture. The rate of biochemical deterioration was more rapid in the traumatic cases than in the average civilian patient with little or no tissue damage. Injury to voluntary muscle was found to be especially important because there was often a rapid rise of plasma-potassium complicated by severe uræmic acidosis due to transfer of intracellular electrolytes from muscle to the extracellular fluid and plasma. Early and oft-repeated hæmodialysis was necessary, whereas non-traumatic cases could often be successfully treated by conservative measures alone. The mortality reported by TESCHAN et al.[9] in 51 wounded soldiers with acute tubular necrosis was 53%.

Subsequent reports on the treatment of traumatic cases in civilian practice have been equally unfavourable. An analysis [10] of 791 cases collected from nine centres showed a total mortality-rate of 43%. PARSONS and MCCRACKEN [11] report that of 25 patients with acute tubular necrosis due to complications of pregnancy or parturition only 2 died, whereas of 25 in whom the cause was accidental injury or surgical operation 18 died. BLUEMLE et al.[12] have analysed 100 consecutive cases of acute tubular necrosis treated in the University of Pennsylvania School of Medicine in the past ten years. They subdivide the cases into a "favourable" group, due to transfusion hæmolysis or to obstetrical complications, with a mortality of 27%; an "intermediate" group, due to poisoning with nephrotoxic drugs or to miscellaneous causes, in which 50% died; and an "unfavourable" group, due to accidental injuries or surgical operations, with a fatality-rate of 73%. A retrospective analysis of the series reported by SWANN and MERRILL [13] gave an almost identical result.

BLUEMLE et al. give a valuable detailed account of the causes of death in their cases. They consider that infection was the most important single factor and that this played a major part in 72% of the fatalities. Pneumonia and tracheobronchitis were the commonest types of infection, followed by intra-abdominal sepsis and septicæmia. Urinary-tract infections, which were common, did not prove immediately fatal in any patient; but in some the infection may have caused permanent renal damage. 5 patients are reported to have died from hyperkalæmia before hæmodialysis could be arranged. (This should now be a rare cause of death in advanced communities; but most centres equipped for hæmodialysis still find that patients are often transferred for treatment too late—sometimes almost moribund.) Non-infective cardiopulmonary complications and disturbances of the central nervous system, including coma and uræmic convulsions, were also of considerable importance. Excessive bleeding was troublesome, and sometimes prevented or delayed hæmodialysis. As in other studies, the causes of the hæmorrhagic tendency were varied, and included reduction of blood-platelets and deficiency of several plasma-coagulation factors. Delayed wound healing was another troublesome complication, and partial or complete dehiscence of abdominal incisions occurred in 5 cases. In a further 6 patients fistulæ developed after abdominal operations. STEIN and WIERSUM [14] have studied rupture of abdominal incisions from another angle. They found that the incidence of dehiscence in abdominal incisions in a single hospital over an eleven-year period was 0·42%. The mortality-rate in these patients was 23%. In all the fatal cases where adequate information was available, there was postoperative acute oliguric renal failure with severe urea retention and typical tubular lesions at necropsy.

In this week's issue Dr. LOUGHRIDGE and her colleagues report on the clinical course of uncomplicated acute tubular necrosis due to obstetric and medical causes. They record mortality figures similar to those in previous series and have selected the more favourable group of cases for analysis. In these the course of the disease was found to be more regular and predictable, and therefore more suitable for statistical analysis, than in the cases due to trauma or surgical operations. The modern tendency to restrict fluid intake to 500 ml. more than the measurable fluid loss of the previous day is shown to be an improvement on previous methods involving a more generous allowance. The average duration of the uræmia was five weeks, but at the end of this period the patients were still invalids incapable of normal activities. This series should prove a useful control for a similar analysis of the more serious group

1. Lowe, K. G. *Lancet*, 1952, i, 1086.
2. Finkenstaedt, J. T., O'Meara, M. P., Weller, J. M., Merrill, J. P. *J. clin. Invest.* 1953, **32**, 567.
3. Edwards, K. D. G. *Aust. Ann. Med.* 1959, **8**, 195.
4. Strauss, M. B. *New Engl. J. Med.* 1948, **239**, 693.
5. Bull, G. M., Joekes, A. M., Lowe, K. G. *Lancet*, 1949, ii, 229.
6. Kolff, W. J. New Ways of Treating Uræmia. London, 1947.
7. Strauss, M. B., Raisz, L. G. *Arch. intern. Med.* 1955, **95**, 846.
8. Meroney, W. H., Herndon, R. F. *J. Amer. med. Ass.* 1954, **155**, 877.
9. Teschan, P. E., Post, R. S., Smith, L. H., Jr., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P., Rush, B. F., Jr. *Amer. J. Med.* 1955, **18**, 172.
10. Proceeding Study Group on Acute Renal Failure. Cited by Bluemle et al. (footnote 12).
11. Parsons, F. M., McCracken, B. H. *Brit. med. J.* 1959, i, 740.
12. Bluemle, L. W., Jr., Webster, G. D., Jr., Elkinton, J. R. *Arch. intern. Med.* 1959, **104**, 180.
13. Swann, R. C., Merrill, J. P. *Medicine, Baltimore*, 1953, **32**, 215.
14. Stein, A. A., Wiersum, J. *J. Urol.* 1959, **82**, 271.

of cases with acute tubular necrosis of traumatic origin. It is still uncertain whether the graver prognosis of the surgical cases is due entirely to the associated injuries and consequent increased liability to infection. Possibly the injuries may prolong the uræmia either by continuing renal damage or by increasing the rate of breakdown of endogenous protein to urea and other nitrogenous waste-products.

Modern Medicine in Ancient Societies

" Too often man assumes that he can manipulate nature freely and without consequence; hence the grand effort to wipe out disease." [1]

WHEREAS immense energy goes into the application of new techniques, comparatively little attention has been paid to their secondary effects; and we are only now beginning to think seriously, for instance, about the consequences of introducing preventive and curative medicine to primitive societies. In present lifetimes the material standards of most developing countries are unlikely to be raised to those of the West; yet modern medicine—or at least the lifesaving drug—is only around the corner. It is encouraging to know that some of the implications of rapid medical improvement, as well as the best ways of achieving it, are now being studied by a team from Cornell University which has been working since 1952 among the Navajo Indians. In a paper, based on his Jenner lecture at St. George's Hospital in July of last year, WALSH MCDERMOTT et al.[2] describe what is being attempted.

The Navajo is the largest of the remaining American Indian tribes, and its culture is remarkably intact. The population of 85,000 is scattered over a vast area (more than 23,000 square miles) of the remote south-western portion of the United States, between the Grand Canyon and the Rocky Mountains—rough country with poor communications and a climate of extremes. Lively and vigorous, the tribe is based on the family and not on the village, and the family groups may be many miles from their neighbours. They live in windowless mud huts with earth floors, a central smoke-hole, and no sanitation. Most of the adults know no English. Although there is a flourishing Navajo religion, an added difficulty for the team is the lack of any written language. Sheep-farming, rug-weaving, and silver-working are the main modes of livelihood, with occasional seasonal work on the railway and farms outside the reservation. MCDERMOTT emphasises the interrelation of things:

" . . . the Navajo stay on their ancestral land and raise sheep thus over-grazing the land so that it blows away and is subject to flash floods which make the roads impassable so that the children cannot get to school to learn English so that they cannot successfully compete in the world outside the Reservation so that of necessity they must stay at home and raise more sheep."

The Cornell group have chosen a district of 800 square miles and a population of about 2000 which returns a representative to the tribal council. A preliminary survey has shown a birth-rate of 48·7 per 1000 and a crude death-rate of 7·3 per 1000 (the corresponding figures for the United States as a whole are 25·0 and 9·6).

At present, perhaps the best means of bringing medical aid to scattered homesteads in vast undeveloped areas is some form of semi-professional worker, carefully trained to advise on hygiene, perform vaccinations and inoculations, distribute simple remedies, and recognise the illnesses which require a doctor. The subassistant surgeon of former days in India was such a person; and so was the old Russian feldsher, who has been retained in the Soviet medical organisation, and still does much of the medical work of the Russian countryside. Less ambitiously, the Cornell group intends to use native " health visitors ", equipped with a car and radio-telephone, four of whom can be controlled by a single nurse or doctor. The difficulties of course are great: the need to transfer concepts from one language to another (particularly when one of the languages is not written); the influence of the traditional medicine-men (though, so far, these have always cooperated with the team); and the danger that when a person is trained in an alien technique he may become as alien as the outsider. Even granted good will, enthusiasm, and supervision of the " health visitors ", there must still be risks in handing, to people of very little education, the means of life or death. As MCDERMOTT et al. remark:

" With today's drugs we can place in the hands of a barefoot illiterate villager more real power to affect the outcome of a child critically ill with, say, meningococcal meningitis, pneumococcal pneumonia, or tuberculosis, than could have been exerted by the most highly trained physician of twenty-five years ago."

But some of the problems can be solved, and some have of course been tackled already in other countries. In the present school year it is hoped to get virtually all the Navajo children into new schools. On the precedent of South Africa, where some of the medicine-men are trained in procedures such as vaccination, perhaps some of the Navajo medicine-men could become " health visitors ". Nor are the trained necessarily so alien to their own countrymen. Sixty years ago an article on Russian medicine quoted a peasant from a remote district:

The doctor—oh! he's the gentleman's doctor, but the feldsher is the *moujik*'s doctor.[3]

The team is studying the patterns of primitive life—in particular anxieties, diet, exercise, sleep, and the consumption of tobacco. Of the diseases they have seen, some three-quarters have been due to infection (particularly streptococcal and tuberculous) and its sequels (e.g., chronic otitis media): gallstones are fairly common, but cancer, hypertension, and myocardial infarction are rare. (Though partly explained by the fact that few Navajo reach middle age, the rarity of myocardial infarction is remarkable, and of special interest because the Navajo diet is rich in animal fat.) To illustrate how much can be done quickly, the success of an anti-tuberculosis programme may be cited.

In 1952 probably some 2–3% of the Navajo had active pulmonary tuberculosis.[4] Arrangements were then made by

1. Gordon, J. E. *Amer. J. med. Sci.* 1958, **235**, 337.
2. McDermott, W., Deuschle, K., Adair, J., Fulmer, H., Loughlin, B. *Science*, 1960, **131**, 197, 280.
3. *Lancet*, 1897, ii, 363.
4. Deuschle, K. *Amer. Rev. resp. Dis.* 1959, **80**, 200.

the Government and the Cornell group to have as many as possible of these patients receive chemotherapy in the small reservation sanatorium and in sanatoria outside the reservation. In 1956 the Cornell team began ambulatory chemotherapy and the tuberculin testing of infants and schoolchildren in the project area. All positive reactors were given prophylactic isoniazid for twelve to eighteen months. As in less backward areas,[5] there was the problem of ensuring that patients took their drugs regularly.

The results from the two programmes were striking. Between 1952 and 1957 mortality from tuberculosis declined by 40%. In the project area, positive tuberculin reactions in children between 5 and 10 fell from 33% in May, 1956, to 22% two years later, while the low incidence of reactions in the school "beginners" class in the autumn of 1958 was even more significant. Of the 49 children only 8 (16%) were tuberculin-positive, and all but 2 of these were already known to be reactors. DEUSCHLE [4] regards this and the absence of miliary or meningeal disease in young children as evidence that tuberculosis is coming under control in the community.

In theory, a developing community might be able to enjoy the "best of both worlds" during the phase when the benefits of modern medicine and of traditional culture are seen together; and there are signs that this is happening to the Navajo. When this period is over, however, they will not necessarily develop the present Western pattern of disease; for, as GORDON [6] says,

"A new influence introduced into the (ecological) system can disrupt the established balance, and set off a new succession whose ultimate end is difficult to predict."

Answers to some of the questions raised in this investigation will be applicable to developing countries outside North America. The Navajo microcosm, situated inside the richest economy in the world, cannot accurately represent the macrocosms of present-day Asia and Africa; but they have many things in common. In particular, the possibility of real harm from too rapid or too enthusiastic technological change must never be forgotten anywhere. MCDERMOTT quotes Mr. GEORGE KENNAN [7]:

"Wherever the authority of the past is too suddenly and too drastically undermined—wherever the past ceases to be the great and reliable reference book of human problems—wherever, above all, the experience of the father becomes irrelevant to the trials and searchings of the son—there the foundations of man's inner health and stability begin to crumble, insecurity and panic begin to take over, conduct becomes erratic and aggressive. These, unfortunately, are the marks of an era of rapid technological or social change."

5. Dixon, W. M., Stradling, P., Wootton, I. D. P. *Lancet*, 1957, ii, 871.
6. Gordon, J. E. *Amer. J. med. Sci.* 1958, **235**, 341.
7. Kennan, G. Realities of American Foreign Policy. Princeton, 1954.

Annotations

PRIVATE PATIENTS IN THE NATIONAL SCHEME

THE Government are being strongly pressed to allow practitioners to prescribe National Health Service drugs for their private patients. The case is arguable, and it is argued with conviction by many who believe in revival of private practice as a remedy for current ills. Everybody, indeed, must see something harsh in a system which says that, because a person prefers to get his medical help from a doctor outside the National Health Service, or to consult an N.H.S. doctor privately, he cannot have the medicines which, as a taxpayer, he has helped to provide.

The British Medical Association has long maintained that he ought to have them; but it recognised that safeguards would be required before purely private doctors could distribute public property. Accordingly, in December, 1958, it agreed that private patients wanting to use N.H.S. drugs should be registered on a list with the local executive council, and that, in respect of them, private doctors would submit to the same code of conduct and penalties as apply to their N.H.S. colleagues. Unfortunately, simple though this solution sounds, it is not really simple at all. For, though the doctors concerned might continue to think of themselves as private, they would in point of fact be entering the Health Scheme—and entering it without accepting payment by capitation. Even though the patient would be paying his doctor privately, the arrangement would amount to Government recognition of the fee-for-service system.

For our part we trust that, before acting on such a plan, the Government will look at more than its financial implications. Much importance has rightly been attached to the principle that, within the National Health Service, medical privileges cannot be bought. (The apparent exception—the private bed in a hospital—is not really an exception at all: the patient in a pay-bed is paying at least the full cost of his treatment; and, though the bed, with services, are rented to him by the N.H.S., he is in fact being treated at his own cost by his own doctor, outside the service.) The proposal now made is that, *within* the national scheme, patients, by paying fees, shall be able to buy the doctor's time, and the convenience of access to him, which are so important a part of good personal care. Since the commonest criticism of N.H.S. general practice today is that it often fails to provide these things, a great many people might be willing to buy them. Yet we all know that good personal care ought to be provided for everybody who needs it—not sold. Surely the last thing we should now do is to establish within the service a group of people who are engaged in selling care of a higher standard, and who therefore have a vested interest in preserving the defects of ordinary medical care? What we need to do, on the contrary, is to give all practitioners a vested interest in getting rid of those defects.

If the capitation system of payment is really a bar to the necessary improvement, let us change it. But whatever else we decide on, do not let us have within the national scheme two levels of medical attention—a new and better one for those who consult their doctor privately, and another for those who do not.

STEROIDS AND ECZEMA

DERMATOLOGISTS can count among their blessings the accessibility of the skin, which enables them to paint, anoint, or spray their patients with steroids. The effectiveness of these measures in many cases of eczema is manifest, and Nordin,[1] who has studied the toxicity of steroids, advises dermatologists to content themselves with topical application whenever possible. It would be premature, however, to assume that topical application never carries a risk, though it is clearly safer than systemic treatment. Nordin found up to 8% mortality attributed to systemic steroid treatment in 11 reported series, one of

1. Nordin, B. E. C. *Brit. J. Derm.* 1960, **72**, 40.

which [2] concerned 200 patients who suffered from a wide variety of dermatoses including pemphigus, of whom 22 had serious complications and 7 died. But the significance of these findings is doubtful, since no distinction was made between those on high life-saving doses and those on small suppressive ones.

The lives of patients on systemic steroid treatment are threatened in various ways:[3] their gastrointestinal tracts may perforate or bleed: they are prone to intercurrent infections, whose symptoms are masked, or to recrudescence of latent infection; they are probably particularly susceptible to thromboembolic catastrophes; and they are liable to a number of other potentially serious complications. In view of this catalogue of iatrogenic disaster and suffering it is natural that Cronin and Wells [2] were extremely reluctant to treat with systemic steroids atopic eczema (Besnier's prurigo), which is not a fatal disease. Nevertheless Sneddon [4] felt from his experience that the dangers of suppressive doses might have been exaggerated. He has given steroids to 26 patients with atopic eczema, selected from 500 for their severity, their failure to respond to other treatment, including topical steroids, and their freedom from tuberculosis, hypertension, and dyspepsia. The treatment has continued for periods of up to $4\frac{1}{2}$ years, and the daily maintenance dose was usually between 5 and 15 mg. of prednisolone. In 19 patients the result was good and in 5 fair. No serious complications arose, but most patients have become plumper. Infection or emotional stress required a temporarily increased dose of steroid, and the risks of surgery have been partly met by issuing a warning card to all patients and urging them to produce it if they consult a surgeon.

The patients improved in personality and coped with life more easily, a change reflecting perhaps the great influence of the dermis on the psyche, as well as the heavy burden of cutaneous misery which such patients carry. Lamont,[5] who reported a somewhat similar series, concluded that the prospect of having to continue treatment indefinitely might make the physician prefer other measures. But it seems that this method might well help selected patients with atopic eczema as nothing else could. If further study confirms its good effects and comparative safety it could truly be said that the disease was worse than the effects of suppressing it. Until then it would be wise to remember Sneddon's final sentence: "... some harmful effects may yet arise and treatment should not be embarked upon lightly or in the absence of adequate facilities for close supervision."

COLD-FOOT SYNDROME

THE typical pain of myocardial infarction may be overshadowed by syncope, shock, vomiting, or dyspnœa; but Wood [6] believes that only 5% or less of patients who are carefully questioned deny the presence of pain or some oppressive sensation in the chest during the acute attack, and Roseman [7] could discover only 5 entirely painless infarcts in a series of 220 patients. On the other hand the observations of Stokes and Dawber [8] and of Weitzman and Smith [9] show that myocardial infarction can apparently occur without any symptoms and be completely silent. Infarcts complicating surgical operations are particularly liable to be overlooked [10 11] because pain is often suppressed by anæsthesia or analgesic drugs,[12] and the picture may be one of shock or persistent hypotension.

Frank [13] has described the syndrome of "cold foot", which may be the presenting sign of an otherwise silent postoperative myocardial infarction. According to Frank the discovery in the postoperative period of a cold foot on one side, often numb or painful, associated with absent arterial pulsation and with ischæmia on elevation, almost invariably indicates myocardial infarction if the heart rhythm is normal and murmurs are absent. The syndrome is, of course, the consequence of arterial embolism in the leg, and, as Haimovici [14] has shown, the vast majority of emboli originate in the heart: less common causes are dislodgment of atheromatous aortic plaques, thrombi arising in the pulmonary veins, and, very rarely, paradoxical embolism through a septal defect. Primary arterial thrombosis is unlikely unless there is pre-existing vascular disease in the lower limbs. Consequently if atrial fibrillation, rheumatic heart-disease, or bacterial endocarditis can be excluded, recent myocardial infarction is the probable cause. Frank has detected the syndrome in 3 patients, 5, 7, and 13 days after abdominal operations: in all 3, electrocardiography confirmed recent infarction. Like Wasserman et al.[12] he believes that anæsthesia or postoperative analgesics may prevent appreciation of the pain of myocardial infarction, but he also points out that when pain is felt it may be wrongly attributed to the discomfort of an abdominal wound.

THE ALBEMARLE REPORT

THE fundamental and inescapable conflict in teenagers stems from the fact that biological maturity is reached so much sooner than social fulfilment. There is nothing new in this. What is new is the influence of the changing pattern of our culture—especially the mass media of communication. The resulting strains have thrown into relief the difficulties of the years of transition. The challenge to society is full of opportunities.

Enthusiasm runs through the fascinating report of the Albemarle Committee,[15] published last week. This committee was set up by the Minister of Education in 1958 with the following terms of reference:

"To review the contribution which the Youth Service of England and Wales can make in assisting young people to play their part in the life of the community, in the light of changing social and industrial conditions and of current trends in other branches of the education service; and to advise according to what priorities best value can be obtained for the money spent."

In critical terms the report notes the failure of successive Governments to provide the means of bringing the youth service properly to life. Reaching only one teenager in three its chief strength has been voluntary help. In 1957–58 for each £1 the Government spent on education only 1*d.* was available for the youth service. Small wonder that its development has been haphazard and that its present condition gives rise to anxiety. Whether or not it is "dying on its feet" the committee acknowledges that it is "in a state of acute depression". To the diffi-

2. Cronin, E., Wells, G. C. *Trans. St. John's Hosp. derm. Soc. Lond.* 1958, no. 40, 26.
3. De Mowbray, R. R. *Postgrad. med. J.* 1957, **33**, 632.
4. Sneddon, I. B. *Brit. J. Derm.* 1960, **72**, 1.
5. Lamont, I. C. *ibid.* p. 7.
6. Wood, P. Diseases of Heart and Circulation. London, 1956.
7. Roseman, M. D. *Ann. intern. Med.* 1954, **41**, 1.
8. Stokes, J., Dawber, T. R. *ibid.* 1959, **50**, 1359.
9. Weitzman, D., Smith, E. B. *Brit. med. J.* 1959, ii, 162.
10. Paton, B. C. *Amer. J. Med.* 1957, **23**, 761.
11. Johnson, W. J., Achor, R. W. P., Burchell, H. B., Edwards, J. E. *Arch. intern. Med.* 1959, **103**, 253.
12. Wasserman, F., Bellet, S., Gaichek, R. P. *New Engl. J. Med.* 1955, **252**, 967.
13. Frank, N. *J. Amer. med. Ass.* 1959, **170**, 1147.
14. Haimovici, H. *Angiology*, 1950, **1**, 20.
15. Ministry of Education: The Youth Service in England and Wales. Cmnd. 929. H.M. Stationery Office. 1960. Pp. 135. 6*s*.

culties caused by lamentably inadequate money, drab and unimaginative premises, and a catastrophic shortage of adult helpers with the right training and outlook have been added the effects of " the bulge ", the ending of National Service, and the social significance of young people with £3 or more spending money a week in their pockets. Against this background, and aware of a " new climate of crime and delinquency ", the committee proclaims and justifies a belief in the immense contribution a youth service can make. This contribution can be made only if the service is expanded and continuously nourished: meanwhile we must rely on short-term, emergency " blood-transfusion " methods.

The four great needs are an imaginative and vigorous approach, money, greatly improved premises, and a large increase in trained workers. The committee proposes the establishment of a Youth Service Development Council, numbering not more than a dozen, to advise and help the Minister. A ten-year development programme, starting this year, is recommended; the first half would be devoted to catching up with events, and the second to establishing a permanent structure on firm ground. Local education authorities are recognised as having a crucial role in the growth of what, after all, is part and parcel of full education for living. Arrangements for providing the necessary leaders are considered in detail. A proposed emergency training college would increase the present force of 700 full-time leaders to a provisional 1300 by 1966. Part-time workers, both paid and voluntary, clearly have an important part.

If these recommendations are implemented there will be real grounds for hoping that the needs of the young generation can be met constructively. Implicit in the committee's approach is the conviction that the Government really does intend to make the youth service adequate; and the Government's acceptance of the main proposals is encouraging.

PSEUDOMONAS AND POLYMYXIN

ONLY a concerted hospital policy, such as that initiated by Barber and her colleagues [1] at Hammersmith Hospital, is likely to stem the increase of resistant strains of staphylococci in our hospitals. The shadow of a further danger—an increased incidence of gram-negative infections, particularly with *Pseudomonas pyocyanea*—was cast by the results of the twenty-two-year survey conducted by Finland and his colleagues at the Boston City Hospital,[2] where there has been a sixfold increase in gram-negative septicæmias since the introduction of antibiotics. The situation is similar in British hospitals, as is pointed out on a later page of this issue by Dr. Roger Williams and his coworkers, who noted an upsurge of *Ps. pyocyanea* infections in Hammersmith Hospital during 1959. Whereas in the first quarter of 1958 only 9 patients were known to have this organism in their sputum, it was found in the sputum of more than 60 patients during a similar period in 1959. In one general medical ward pseudomonas infections were responsible for 5 deaths, and, in addition, sporadic cases of localised infection and of septicæmia arose throughout the hospital. Poor resistance undoubtedly contributed to the 5 deaths; for 2 patients were leukæmic, 1 had agranulocytosis, another was in respiratory failure, and the 5th was receiving long-continued oral corticosteroids on account of hæmolytic anæmia. But Williams et al. suggest that the increase may also be related to the doubled consumption of tetracycline and other broad-spectrum antibiotics.

The only antibiotic that combats pseudomonas infection really effectively is polymyxin. This was isolated independently in Britain [3] and in the United States [4 5] from *Bacillus polymyxa*, and in this country was originally known as 'Aerosporin' (its present trade name.) It is now available as polymyxin B sulphate powder in vials containing 500,000 units. It may be given by mouth and by intravenous, intramuscular, intrathecal, subconjunctival, and intrapleural routes. There are various topical preparations, and a 0·1 to 1·0% saline solution may be used to irrigate sinus tracts. Polymyxin, which is not absorbed from the gut, may be given by mouth for bowel infections which do not respond to sulphonamides, streptomycin, or neomycin. Since it does not affect the gram-positive intestinal flora, monilia and other fungi do not emerge as dominants. For systemic infections, it is administered intramuscularly in a dose of 20,000 units per kg. daily, an average dosage for adults being 250,000 units four-hourly. Because of pain at the site of injection, it should be administered with procaine and the site frequently changed. During treatment with polymyxin, the urine should be examined daily for albumin and casts; and the blood-urea level should be estimated twice weekly as the drug is potentially nephrotoxic. The indication for its use in severe infections that resist other antibiotics usually outweighs the risk of toxicity. This risk has hitherto prevented its widespread use: which can now be counted as a blessing, for otherwise *Ps. pyocyanea* might not be still sensitive to the drug. Polymyxin should on no account be used for the treatment of trivial hospital infections.

CONGENITAL MALFORMATIONS

FROM many sides, the pathogenesis, the possible prevention, and the treatment of congenital malformations are getting more and more attention: as postnatal infections come under control, what has been called prenatal pædiatrics is gaining in relative importance. The time is ripe therefore for the first International Congress on Congenital Malformations, and we are glad that it will be held here in London next July.

The honorary presidents are to be the Hon. Basil O'Connor and Sir Geoffrey Marshall, and the general chairman Prof. J. D. Boyd, of Cambridge. Meeting at Church House, Westminster, on July 18, the congress will have a theme address from Dr. George W. Corner; and will spend five days on sessions entitled: Incidence; Intrinsic Factors (genetics); Extrinsic Factors (environment); General Developmental Mechanisms; Abnormal Developmental Mechanisms; Maternal-Fœtal Interactions; Physiological and Medical Problems; and Perspectives. The executive secretary and treasurer of the congress is Mr. Stanley E. Henwood, and his office is at 67, New Bond Street, London, W.1.

The report of the Royal Commission on Doctors' and Dentists' Remuneration will be published on Feb. 18.

Prof. E. J. WAYNE has been appointed chairman of the clinical research board of the Medical Research Council in succession to Sir Geoffrey Jefferson, who has retired after a six-year term of service as first chairman of the board.

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2. Finland, M., Jones, W. F., Barnes, M. W. *J. Amer. med. Ass.* 1959, **170**, 2188. See *Lancet*, Jan. 16, 1960, p. 157.
3. Ainsworth, G. C., Brown, A. M., Brownlee, G. *Nature, Lond.* 1947, **160**, 263.
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Special Articles

CROSS-INFECTION WITH PSEUDOMONAS PYOCYANEA

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Pseudomonas pyocyanea is well known as a relatively avirulent secondary contaminant of superficial wounds and burns; but more serious infections may occur, particularly in infants or in adults whose resistance is weakened by other disease. This organism tends to be resistant to the commonly used antibiotics, and with the widespread use of these agents there is some evidence that the incidence of infection with *Ps. pyocyanea* is increasing.

Yow (1952) traced 56 examples of infection due to *Ps. pyocyanea* or proteus during or following antibiotic therapy over a two-year period. On analysing the routine cultures received in the bacteriology department during this time he found that the incidence of *Ps. pyocyanea* had risen from 15% of the gram-negative bacilli isolated to 30%. In children with mucoviscidosis Garrard et al. (1951) observed that the decrease in frequency of staphylococcal infections was accompanied by an increase in those due to *Ps. pyocyanea*.

During the past year we have experienced in this hospital a disturbing incidence of cross-infection with *Ps. pyocyanea*, and we draw attention here to some of the problems involved. In one general medical ward alone, pseudomonas infection was responsible for 5 deaths. These are described together with studies of the probable source of infection and mode of transmission.

Case-reports

Only a brief account of the clinical course is given as the main bacteriological and pathological findings are shown in table I.

Case 1.—A man of 22 was admitted in May, 1958, with acute leukæmia. After three weeks' treatment with 6-mercaptopurine the white-blood-cell count had fallen to 1800 per c.mm. (polymorphs 5%). He then developed a fever up to 104°F and signs of bronchopneumonia, the sputum growing *Ps. pyocyanea* in pure culture. There was no response to antibiotics (including streptomycin) and he died three weeks after the onset of fever.

Case 2.—A man aged 54 was admitted in July, 1958, with polyarthritis, fever, and agranulocytosis, this last being attributed to phenylbutozone which he had been given two months earlier. Although the arthritis responded to salicylates the fever continued, and a chest X-ray showed pneumonic shadowing in the left upper zone. There was some response to antibiotics (penicillin and streptomycin) and prednisolone, but when the antibiotics were discontinued the fever recurred. Finally at the beginning of August numerous papular skin lesions appeared over the trunk and limbs; many of them became nodular with dusky red hæmorrhagic centres increasing in size up to 1 in. in diameter. At this stage *Ps. pyocyanea* was isolated. The patient died on Aug. 10, three weeks after admission.

Case 3.—A 59-year-old man, a known case of chronic lymphatic leukæmia, was readmitted in October, 1958, with acute cholecystitis. The white-cell count on admission was 4000 per cm. (polymorphs 10%). His symptoms subsided rapidly with antibiotics (tetracycline and erythromycin) but he then developed a sore throat followed a few days later by pseudomonas septicæmia. This responded initially to streptomycin, but later the fever recurred and laparotomy was performed. This revealed an empyema of the gallbladder which was drained, but the fever continued and despite systemic polymyxin he died three days later.

Case 4.—A man of 50 with a long history of chronic bronchitis and emphysema was admitted in December, 1958, with an acute exacerbation. After an emergency tracheostomy and bronchial aspiration treatment was continued with intravenous hydrocortisone and antibiotics (penicillin and streptomycin). He improved dramatically at first but on the morning of the third day after admission his temperature rose to 104°F. *Ps. pyocyanea* was now present in the sputum, and he died later the same day.

Case 5.—A man, aged 79, with acquired hæmolytic anæmia had been maintained on prednisolone (20 mg. daily) since June, 1957. He was readmitted in September, 1958, with fever and a mass in the right lung presumed to be a carcinoma. He was treated with radiotherapy and antibiotics (tetracycline and novobiocin) but developed pseudomonas diarrhœa. This did not respond to neomycin, and profuse watery diarrhœa persisted until his death in peripheral circulatory failure on Dec. 11.

MICROSCOPICAL FINDINGS

The histological appearances of the septicæmic lesions in the first 3 cases were basically similar with an area of central necrosis, in which traces of pre-existing structure remained, surrounded by a narrow inflammatory zone

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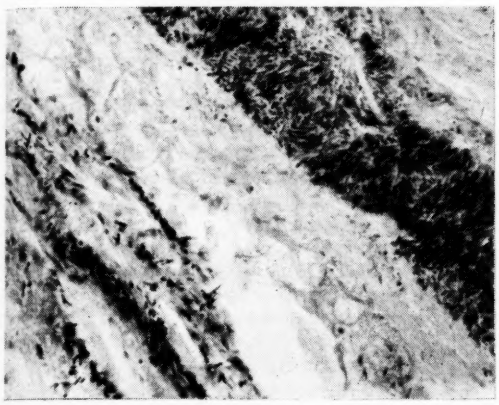
TABLE I—BACTERIOLOGICAL AND PATHOLOGICAL FINDINGS IN 5 FATAL CASES OF PSEUDOMONAS INFECTION

Case no.	Pseudomonas cultures during life: Specimen	Antibiotic sensitivity pattern: P	STR	T	C	N	Poly.	Necropsy cultures (pseudomonas)	Relevant postmortem findings
1	Sputum	R	R	R	R	..	S	Liver, lungs, kidneys	Multiple small septic infarcts in liver, lungs, and kidneys
2	Blood Skin biopsy	Not done "						Lungs	Multiple firm nodules in lungs; small abscesses in kidneys; multiple skin nodules
3	Throat swab Blood (1st episode) Blood (2nd episode) Empyema pus	.. ..	S S R R	.. .. R R	R .. R R	.. .. S S	S S S S	Pus in paracolic gutter	Acute cholecystitis; peritonitis; small abscess in prostate; multiple small nodules in pleura, and two larger ones in right upper lobe
4	Bronchial aspirate	R	R	R	R	..	S	Right lung	Acute bronchitis; confluent bronchopneumonia on right side
5	Stool	..	R	..	R	S	S	Not done	Numerous yellow ulcers up to 0·8 cm. in diameter throughout large intestine

P=penicillin. STR=streptomycin. T=tetracycline. C=chloramphenicol. N=neomycin. Poly.=polymyxin. R=resistant. S=sensitive.



High-power view of the wall of an artery adjacent to a pulmonary lesion in case 1. Innumerable bacilli are seen in the artery wall, and small numbers are present in the antemortem thrombus in the dilated lumen (lower left). (Acid fuchsin/picric acid. ×950.)

containing relatively few polymorphs and much granular debris. Gram-negative bacilli were present in the periphery of the lesions and were also seen in very large numbers in the walls of adjacent small arteries (see figure). Some of these were occluded by antemortem thrombus, and in the 1st case a small mycotic aneurysm was found near one of the pulmonary foci. The skin nodules in case 2 showed a similar histological picture to the visceral lesions, and numerous bacilli were present in the wall of an adjoining artery. The lung lesions in case 3, though similar in distribution and histological structure to those in the first 2 cases, did show some surrounding fibrosis, and it seems likely that these were the result of a previous septicæmic episode (particularly as shadows corresponding to the site of these had been noted in a chest X-ray taken six months before death when the patient was admitted with pyrexia of unknown origin.)

In the other 2 cases there was no evidence pathologically of septicæmia. In case 4 the bronchopneumonia was remarkable on microscopy for the poor cellular reaction and the numerous gram-negative bacilli in the alveolar exudate. Similarly in case 5, despite the widespread ulceration, there was only a slight cellular reaction consisting mainly of plasma cells.

Sources of Infection

Infection with *Ps. pyocyanea* was not restricted to this one ward, and sporadic cases both of localised infection and of septicæmia occurred throughout the hospital during the year. We have described only those cases occurring in the one ward as more information is available there regarding the mode of transmission and possible sources of infection.

It seems likely that infection was airborne, for bacteriological studies showed a high concentration of *Ps. pyocyanea* in the air. Also pneumonic signs were present at an early stage in cases 1, 2, and 4—suggesting a portal of entry via the respiratory tract, and in case 3 the organism was first demonstrated in a throat swab. In keeping with this mode of transmission the main source of infection appeared to be sputum. Table II shows details of all the patients in the ward during the year who had sputum from which *Ps. pyocyanea* was isolated. These were mainly cases of chronic respiratory disease, and the organism appeared in the sputum as they were improving clinically after a course of broad-spectrum antibiotics. 4, however, had not been treated with antibiotics. Although in these the organism was cultured from the first specimen examined, this had not been sent until several days after admission; so the infection may well have been acquired in the ward. It can be seen from table I that apart from February, March, and April there were always one or two patients in the ward with sputum containing *Ps. pyocyanea*. The first of the patients who died later of pseudomonas septicæmia was admitted soon after a patient with bronchiectasis whose sputum consistently yielded a heavy growth of this organism.

It is apparent from the varying antibiotic sensitivity pattern of the organisms isolated (tables I and II) that the infections both in the fatal cases and in the patients with respiratory disease could not be attributed to a single strain and probably several were involved.

Discussion

The first 3 cases show many of the distinctive clinical and pathological features of pseudomonas septicæmia. Although in case 1 a positive blood-culture was not obtained in life, there were at necropsy widespread septicæmic lesions from which *Ps. pyocyanea* was cultured in pure growth. Fraenkel (1917) originally stressed the tendency of this organism to multiply in the walls of small blood-vessels, producing acute inflammatory arteritis. Secondary thrombosis leads to arterial occlusion and the formation of small infarct-like areas of necrosis, which were such a striking feature of the present cases. Characteristic skin lesions may occur in pseudomonas septicæmia and may be of help in early diagnosis. These (as in case 2) begin as macules or papules and later form round indurated areas with black necrotic centres from which the organism

TABLE II—DATA ON ALL THE PATIENTS IN THE WARD DURING THE YEAR WHO HAD SPUTUM FROM WHICH *Ps. Pyocyanea* WAS ISOLATED

Patient	Diagnosis	Present on admission	Date first isolated	Previous antibiotics	Growth	Antibiotic sensitivity pattern					
						P	STR	T	C	Poly.	Sul.
A	Chronic bronchitis	No	Jan. 13	Chloramphenicol	++	..	R	S	S	..	..
B	Bronchiectasis	No	May 14	Penicillin, chloramphenicol, tetracycline	+++	R	S	R	R	S	R
C	Leukæmia	No	June 16	Tetracycline and novobiocin	++	R	R	R	R	S	S
D	Lung cancer	..	June 23	None	+	..	S	R	R	..	..
E	Chronic bronchitis	..	July 12	None (during this admission)	++	..	S	R	R	S	..
F	Lung abscess	No	Aug. 7	Tetracycline and novobiocin	++	..	S	R	R	S	..
G	Chronic bronchitis	No	Sept. 9	Novobiocin and chloramphenicol	+++	..	S	R	R	S	..
H	Mitral stenosis	..	Sept. 9	None	++	..	S	R	R	S	..
I	Lung abscess	No	Oct. 11	Erythromycin and novobiocin	+	R	S	R	R	S	R
J	Asthma	..	Oct. 18	None	+++	..	S	R	R	S	..
K	Chronic bronchitis	No	Oct. 22	Chloramphenicol and novobiocin	+++	..	..	R	S	..	..
L	Lung cancer	No	Nov. 11	Tetracycline and novobiocin	+++	..	S	S	..	..	..
M	Cardiac infarction	..	Nov. 19	None	+	..	S	R	..	..	..
N	Pneumonia	..	Dec. 5	Penicillin, streptomycin, chloramphenicol	++	R	R	R	..	S	..
O	Bronchiectasis	No	Dec. 15	Tetracycline and novobiocin	++	..	R	R	R	S	R
P	Chronic bronchitis	No	Dec. 31	Tetracycline and sulphonamide	++	..	R	R	R	S	S

P=penicillin. STR=streptomycin. T=tetracycline. C=chloramphenicol. Poly.=polymyxin. Sul.=sulphonamide. R=resistant. S=sensitive.

can easily be cultured. In a recent series of 23 cases of pseudomonas septicæmia (Forkner et al. 1958) skin lesions were present in 9.

In the other 2 cases the infection remained localised and bloodstream invasion did not occur. In case 4 secondary infection with *Ps. pyocyanae* was probably responsible for the clinical deterioration after the earlier response to treatment. In case 5 the severe diarrhœa undoubtedly contributed to death. Although *Ps. pyocyanea* may be isolated occasionally from routine stool cultures, the number of organisms is small and, in those cases where tissue invasion occurs with ulceration of the mucosa, as in this patient, large numbers are seen; at times as many as 50–75% of the colonies isolated are of this organism (Stanley 1947).

Each case had previously been treated with broad-spectrum antibiotics. This is in keeping with the role of *Ps. pyocyanea* as a secondary or superinfecting organism. Forkner et al. (1958) found that 77% of pseudomonas septicæmias occurred in patients receiving broad-spectrum antibiotics, whereas only 33% of those due to staphylococci occurred under such circumstances. Experimentally, in mice both cortisone and radiation increase the susceptibility to pseudomonas septicæmia (Ross 1956, Millican et al. 1957), and there is suggestive evidence in man that anti-metabolite administration may be another predisposing factor (Forkner et al. 1958). All our cases had received corticosteroids, and case 1 and 3 anti-metabolites, although in case 3 this was many months previously.

The occurrence of a normal or low white-cell count in both localised and bloodstream infections with *Ps. pyocyanea* has been recognised since 1899 when Ghéorghiewsky claimed to have found a leucocyte-destroying ferment in cultures of this organism and Brill and Libman remarked on the absence of leucocytosis in 2 cases of pseudomonas septicæmia. Later, several workers (Lovett 1924, Linthicum 1927, Dasse 1928) isolated this organism from the local lesions and occasionally from the bloodstream of some cases of agranulocytic angina and showed experimentally in guineapigs that it had a direct lytic effect on leucocytes and possibly also an inhibitory effect on their formation in the bone-marrow. On the other hand, patients with low white-cell counts are abnormally susceptible to infection and may be particularly liable to pseudomonas septicæmia. Forkner et al. (1958) found that *Ps. pyocyanea* was the most frequent bacterial cause of death in leukæmia and the second most frequent cause of septicæmia. Many factors other than a low polymorph-count may, however, contribute to the diminished resistance in acute leukæmia, including abnormal antibody response and altered phagocytic properties of the leucocytes (Silver et al. 1960). 2 of our patients had leukæmia and the 3rd marrow asplasia probably secondary to phenylbutazone toxicity, and in all 3 the neutropenia preceded the septicæmia. In a fatal case of pseudomonas septicæmia recently in one of the surgical wards, the white-cell count dropped to 2200 per c.mm. on the fourth postoperative day, but by the time of death, two days later, it had risen to 8000 per c.mm.

The high mortality of pseudomonas septicæmia is of course related as much to the underlying disease as it is to the superimposed infection. All but 2 of the 22 fatal cases reported by Forkner et al. (1958) had malignant disease. Other series which include cases with less serious underlying disease have a lower mortality (Martin et al. 1954). The majority of strains of *Ps. pyocyanea* are sensitive only to polymyxin or neomycin. Unfortunately, both these drugs are toxic when administered parenterally, although if careful attention is paid to dosage this risk can be largely averted. Jawetz (1952) used polymyxin B in a dose of 2·5 mg. per kg. body-weight for six days in 35 patients with pseudomonas infections over a two-year period without any nephrotoxic effects; but even when this drug is given in pseudomonas septicæmia the result may be disappointing. In the series reported by Forkner et al. (1958) 9 cases were treated with polymyxin but none improved although in 3 the blood-culture became negative. Occasional strains are also sensitive to streptomycin, but resistance usually develops rapidly as in case 3 of the present series.

There seems to be no doubt that the patients reported here acquired their infection after admission to hospital. Little attention has previously been paid to the problems of cross-infection with this organism in medical wards. Forkner et al. (1958) studied the incidence of septicæmia in 13 patients with leukæmia treated in the same unit over a twenty-month period. They found that septicæmia due to *Ps. pyocyanea* tended to occur in small groups in contrast to the random distribution of other bacterial septicæmias, though the factors responsible for this were not clear. In an outbreak of infantile diarrhœa in a children's ward (Florman and Schifrin 1950) indirect spread via nursing staff was thought to have occurred as the organisms were isolated from the hands of two nurses who shortly before had handled children with positive stool-cultures. An airborne mode of transmission was considered likely in a series of cases of pseudomonas meningitis and penetrating head injuries reported by Botterell and Magner (1945) as a high concentration of *Ps. pyocyanea* was found in the air of the wards, all of which were over-crowded.

The importance of sputum as a reservoir of infection with *Ps. pyocyanea* is shown by the present studies. The appearance of this organism in the sputum of the majority of the patients, described in table II, was not accompanied by any clinical signs of infection. Nevertheless, it is probably from these patients that the more serious infections in susceptible subjects originate. They constitute in this hospital a serious and increasing problem. In the first quarter of 1959 there were more than 60 patients with *Ps. pyocyanea* in their sputum, whereas during a similar period of 1958 there were only 9. It is tempting to relate this increase to the greater use of tetracycline and other broad-spectrum antibiotics, the consumption of which has nearly doubled over the past year.

Various measures may help to prevent cross-infection. Clearly the use of broad-spectrum antibiotics should be limited as far as possible. Patients with this organism in their sputum should be taught to cough directly into a sputum pot containing a suitable disinfectant such as 'Sudol' which has the same bactericidal spectrum as 'Lysol' without its irritant effect. Treatment with inhalations of polymyxin (25,000 units) and neomycin (5 mg.) given four times a day through a Wright nebulizer is sometimes followed by disappearance of the organisms from the sputum, but in our experience systemic polymyxin is necessary in those with a heavy growth. Ideally these patients should be isolated, but this has proved difficult owing to the numbers involved. A more practical measure is to isolate patients with leucopenia from

any cause, who appear to be particularly at risk from cross-infection with *Ps. pyocyanea*.

Summary

Cross-infection with *Ps. pyocyanea* materially contributed to 5 deaths in one ward in 1958.

Predisposing factors appeared to be a low white-blood-cell count and previous treatment with corticosteroids and broad-spectrum antibiotics.

The infection was apparently airborne, and the main source was the sputum of certain patients with chronic respiratory disease.

The frequency of infection with this organism is increasing.

We would like to thank Dr. J. G. Scadding and Dr. P. Hugh-Jones under whose care these patients were admitted for permission to publish this report. We are indebted to Mr. J. Griffin and Miss G. Fisher for histological assistance; and to the bacteriology department for help and particularly to Dr. Mary Barber for advice and encouragement.

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PRESERVATION OF MEDICAL RECORDS

A Memorandum by the British Records Association *

THE medical profession is uncomfortably familiar with the proliferation of papers which modern methods of office administration produce. The resulting accumulation of papers too often provokes periodic indiscriminate destruction, in which records of value and interest, often of some age, may disappear, along with masses of modern ephemeral material. To avoid the ill-effects of unregulated destruction the Association has published memoranda stating general principles for the disposal of records such as are described in its Memorandum no. 7,

Modern Records, what may we destroy?

Since the National Health Service was instituted, certain classes of medical records—e.g., those of hospitals and hospital administration—come under the control of the Minister of Health and are subject to the statutory arrangements for public records. The Ministry issues directions about their preservation and destruction, which are drawn up in consultation with the Public Record Office. The medical records accumulated in health departments of local authorities will, in general, be covered by the arrangements existing within each authority for the preservation of departmental records. The following advice is, therefore, primarily directed to individual practitioners, voluntary hospitals, and other organisations or persons whose records are not covered by the preceding arrangements.

Records may be classed for the purpose of preservation as those of the distant past, those of the immediate past, and present-day records. A convenient division between the distant and immediate past is afforded by the Medical Act, 1858, before which no compulsory system of registration of medical practitioners was enforced. Present-day records may be regarded as beginning with the National Insurance Act, 1911. All records before 1858 should be kept and none of those relating to the period 1858–1911 should be destroyed before advice has been obtained. As regards documents later in date than 1911, the pamphlet *Modern Records, what may we destroy?* provides, in general, adequate guidance. There are, however, two kinds of record which call for special consideration.

First, there are the records of individual doctors. Details of how practices were run, how patients were referred to the doctor, how many he saw in a day, &c., are very difficult to find. Therefore visiting-list books, letters giving details of consultations, and diaries containing professional rather than personal matters, should be looked for and, if possible, preserved. They are, in general, the kind of thing that tends to be destroyed as being apparently of no interest.

Then there is the clinical note, a kind of record peculiar to medicine, of which, over the years, there may be such accumulation that their preservation in entirety is a matter of some difficulty.† But there are special reasons why case-notes *are* of historical value. They are, for instance, the best source for the history of the introduction of the physical examination of patients and of other methods of investigation; of the invention and applications of pathological investigations, such as the chemical testing of urine; of the introduction of bacteriological principles into medical consciousness; and of the development of radio-diagnosis and the introduction of radiotherapy. Case-notes also provide a far more accurate basis for the history of treatment than do textbooks, because they tell what was in fact given to patients, and not what was recommended. Some historical matters (such as the rise and fall of the use of arsenic in internal medicine) would be impossible to elucidate without original records. They also provide first-hand evidence of the changing attitude of doctors to disease at different times, and contain a great deal of intimate detail about habits, food, drink, clothing, housing, and families of patients. Case-notes, therefore, constitute a very accurate and impartial record of social history. There are thus many sound reasons for their preservation as far as is practicable.

It may be physically impossible for the organisation which produces case-notes or other medical records to provide permanent storage for all of them, but every effort should be made to preserve them. The use of scarce office space for the storage of these records may be difficult to justify, but the attic, roof space, or cellar, will provide an alternative " limbo ". If these records can be kept, in whatever order and state (damp excepted), they will at least exist and still be available for the painstaking searcher who desperately needs them.

By their nature, medical records, especially clinical records, are highly confidential, and before allowing them to leave their possession, practitioners and institutions will certainly wish to be assured that this confidential nature will be respected. Certain standard conditions of receipt by archive repositories should attach to accessions of medical records for the protection of all parties. In general, no clinical records should be available for public inspection until a hundred years after the date of the last entry. This term could be varied at the discretion of the

* Copies of this memorandum can be obtained free from the Secretary, Records Preservation Section, British Records Association, The Charterhouse, London, E.C.1.

† In the case of the files in which the clinical notes of each hospital patient are nowadays kept, it will almost certainly be necessary to resort to some process of sampling, a matter which is at present under careful consideration.

archivist in the case of a person conducting bona-fide research on production of evidence of his standing and competence. In no case should names of patients be quoted, and individual cases should not be identified by name in any work published as a result of such research, until after the passage of a hundred years. Persons consulting medical records should be required to give a signed undertaking to observe these conditions before being allowed access to the information. A general condition of deposit in the case of clinical records or case-books would be that those records would only be opened to members of the public subject to the above restrictions. Any lists of the records compiled in the archive repository and placed on open access shelves in search rooms should bear clear statements of these restricted terms of access. It is felt that such conditions, if clearly explained to practitioners and institutions before a deposit were made, would satisfy them that the confidential nature of the records would not be abused. Any other conditions which individual depositors wish to impose would be respected by repositories, insofar as it would be practicable to do so.

The kind of record ‡ to be searched for will comprise:

Foundation deeds, statutes and rules of medical societies and institutions, medical charities and dispensaries, and medical schools.

Minute books of governing bodies and committees.

Ledgers and main accounting records.

Annual reports and balance sheets.

Registers, such as those of students undergoing training or of patients admitted to hospital, where more than the patient's name is given.

Letters written by medical men which may be of professional or personal interest; (the former may prescribe a course of treatment, give an opinion on a case or throw light on medical education; the latter may have biographical value).

Lecture notes, which may provide the only source of information for lectures of distinguished physicians and surgeons and give some indication of the state of knowledge of the time; and other students' notes.

Licences (including letters testimonial) to practise medicine generally or in one of its branches.

Partnership agreements.

Account books and ledgers, which may contain information about the size of a doctor's practice, professional fees, the cost of drugs, &c.

Case books and medical diaries.

Prescription books.

When the fate of any medical records is being considered, it would be wise to enlist the assistance of the Records Preservation Section of the British Records Association, county or borough archivists, the Royal College of Physicians of London, the Royal College of Surgeons of England, the Wellcome Historical Medical Library, or the National Register of Archives, with a view to arranging for their deposit in a suitable repository. In order that medical and social historians, and others, may have ready access to this material, the Royal College of Physicians has agreed to act as a centre of information and advice on what should be kept or what may be found in the various repositories. Copies of any lists of deposited records made by local archivists and reproduced by the National Register of Archives will be sent to the Royal College of Physicians, which will also pass on to the National Register of Archives information about the location of records which it receives. These reports will, of course, be available to students at the central office of the National Register of Archives in Quality House off Chancery Lane, W.C.2, on the same basis as other reports on various types of archives.

‡ Examples of many such records are given in the *Catalogue of an Exhibition of Medical Records* shown in 1958 at the Royal College of Physicians of London (published by the British Records Association, The Charterhouse, E.C.1, price 2*s*. 6*d*.).

In England Now

A Running Commentary by Peripatetic Correspondents

THE other week we were discussing new research projects, and as one of our colleagues is interested in the medical aspects of boxing and another in head injuries, an experimental study of boxing pathology was suggested. Of course this has been done already, but the older technique of creeping up behind some poor animal and hitting it on the head with a blunt instrument could surely be refined. Why not teach apes to box and have them knocked out under conditions of autonomic and endocrine discharge comparable to those of the ring? But someone pointed out that we might run into difficulties. Boxing has been recommended by Professor Whitteridge as a sport eminently suitable for subhuman primates, but the Home Office is likely to disagree and might well refuse to allow such experiments on the grounds that boxing is too cruel a procedure to be used on the animals in relation to the new information likely to be gained. And admittedly it could not be contended that the pathological findings would lead to new medical knowledge—that is, unless anyone has seriously suggested that blows to the head are beneficial to the brain.

* * *

For most husbands sleep is usually firmly on the credit side of the marriage balance-sheet. Deep sleep at night, blissful dozing off in the companionship of an evening by the fireside, a brief nap after lunch until the washing-up is finished. But for wives it seems to be different. Are men really the chief disturbers of the peace, or is it just that the women complain more?

"He sleeps nice enough until two in the morning. Then he gets up and goes downstairs. If that doesn't wake me, it's the pipes rattling as he fills the kettle at the sink. So I lie there, listening to him moving around in the kitchen and wondering what he will be eating this time. At three o'clock he's back in bed again and asleep at once, while with me, it's ages before I can get off. His mother says his father used to be exactly the same."

"Seems at work he has a machine where he pushes something down with his foot and pulls down a lever with his hand. So at night he has to start doing this in his sleep . . . !"

"Well you know what his breathing's like, doctor, and on top of that, cough, cough best part of the night, and if that's not bad enough, he goes and covers his head with the blankets. It's that queer and muffled like, I keep thinking he must be suffocating . . ."

"He snores something really dreadful. I had to move into our Pat's room with her, but we can still hear him through the wall."

"Well, I made a bad mistake. I didn't know when I was well off. Ted's all right, good fun to be out with, but he's jumpy, can't never keep still, even in bed. Then he's sharp with the kids. He smacked our Vera yesterday, right in the middle of Woolworth's, and she gave one scream out, 'I want my dad!' I could have sunk through the floor. Now Nick was dead quiet, a twenty-four-hour-a-day sort of husband, and God help me, he let me sleep."

* * *

A faint reminiscent odour stole on my senses as I sat at the Comitia of the Royal College of Physicians. Ripe apples, acetone bodies, there must be a diabetic close at hand, I reflected, and whispered my suspicion to the colleague on my right, hoping he was not the sufferer. "Can't say I notice it myself," he replied—a heavy smoker perhaps—"But don't you think it might be the nail varnish of the lady on your left?"

* * *

"In winter time you will probably have to travel quite a lot by dog-sledge, and if you have skis bring them along." I left the Minister's office with a vision in my mind labelled "Doctor to the Great White North". Two weeks ago and well into the G.W.N. I was introduced to my first dog-team. The sledge seemed orthodox enough, but there were only three dogs—not the burly huskies of film and book, but a rather apologetic bunch. Two were on their feet, one sat down and looked longingly at home. I shouted "Mush" in an inquiring sort of way. Surely every dog has heard of this word, but not my three. Eventually by taking the lead at the traces I got them moving. No. 3 sat down for quite a while before getting up and trying to run back to the kennel. Some yards further on I tired of running behind the sledge and hopped on to the runners. The whole outfit stopped abruptly, and some mention was made

of the shop steward—at least that is what it sounded like. I climbed off, apologised, took the lead trace, and away we went again. I soon took up my old position behind the sledge and it was two minutes before I noticed that the traces were slack behind the dogs and that I was pushing the sledge across the ice. I made a mental note that I had a lot to learn about driving a dog-team and resolved to take skis the next time. But it was an unhappy occasion. I shot off a snow-bank into the sea and ended my journey complete with skis and some incongruity in the back of a rowing boat. It seems that I have not yet settled the problem of transport.

* * *

I used to step smartly out of the front door on my eager way to work. Now I hesitate on the threshold, cautiously poke my head out, look both ways, and then proceed, only to shy again at the intersection of the garden paths. You see, I have acquired a new conditioned reflex. As an industrial medical officer I have found that it is wise to assume that there is a "stacatruc" round every corner and a lorry at every crossing. It is bad enough walking or driving across a network of railway lines, but at a steelworks you are liable to bump into very hot pieces of metal as you try to avoid great ingots swinging through the air on unpredictable courses. In coal-mines there is usually just time to flatten against the walls when unattended trucks come hurtling along rails that also serve as footpaths.

I would like to put this explanation on record before it is assumed that the nerve of a once-intrepid hockey-player has finally gone. On second thoughts, perhaps it has.

* * *

Our Transatlantic friend is not accustomed to medicine in the Welfare State. Imagine her surprise when she attended the antenatal clinic of a London teaching hospital and Sister said "Can you spend a penny, dear?" As yet unfamiliar with the English idiom, she was only struck by the smallness of the sum. "Sure I can spend a penny" she replied, "but what for?" Sister explained what was wanted. "Oh! Urinalysis ... Gosh, that's cheap. It would cost a dollar fifty back home!"

* * *

Overheard at the Club

"... and he doesn't really know one end of a virus from the other."

* * *

BALLADE OF ACADEMIC INEPTITUDE

Well, no, I hadn't heard of that before;
(Doubtless it's common knowledge to the rest)
Written, you say, in 1834,
And published by a firm in Budapest?
I try not to admit that I'm impressed.
To me such virtuosity comes hard,
But to achieve it I shall do my best;
I write it down upon a little card.

Eager for knowledge, I read books galore,
Though reading tends to make me more depressed
Since each one read suggests a couple more;
Progression geometric spoils my quest.
In any case, I never could digest
So many facts; some I must disregard,
And others are more use if they're compressed.
I write it down upon a little card.

I never shall be a contributor
To learned journals; were I to suggest
A thesis, they would quietly deplore
Such rashness, though I meant it for the best.
It's very hard merely to keep abreast
Of modern trends. I'm always on my guard
Lest I should miss something of interest;
I write it down upon a little card.

Envoi

Prince, my despair shall not be manifest.
In spite of all I'll keep up the facade.
No-one shall know how much I am distressed;
I write it down upon a little card.

Letters to the Editor

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—The report on bretylium tosylate by Professor McMichael and his colleagues in last week's *Lancet* will be of much interest to all concerned with the treatment of hypertension. As they point out, there has been great need of a drug which patients could tolerate with less difficulty than those which act by ganglion blockade. Our experience has been of a similar group of patients treated over a similar period of time, and likewise many had previously been on pentolinium, mecamylamine, or pempidine. In our hands, however, the results have been rather less promising, and the difficulties encountered force the conclusion that while bretylium is certainly an early probe into new territory, it has not been demonstrated over a sufficient period of time that it is a satisfactory drug for the routine treatment of hypertensive patients. While there is no doubt that many of our patients previously treated with ganglion-blocking drugs have expressed pleasure at being relieved of the unpleasant side-effects which were the inevitable accompaniment of treatment, they have been unaware at this stage that their blood-pressures were still uncontrolled or only partially controlled. When serial increases in dosage were necessary or new side-effects began to appear, fewer patients were heard to express satisfaction.

We have found it best to begin with 100 mg. ($^1/_2$ tablet) three times a day because some patients are very sensitive to the drug. It usually takes several weeks or months to determine the optimal dosage.

Difficulties in the control of blood-pressure with bretylium can be classified under three headings—tolerance, instability of the blood-pressure, and side-effects.

(1) *Tolerance.*—A preliminary fall in pressure has been recorded in most cases, but when kept under observation for several months a large proportion of patients (75%) have been found to require a steady increase in the dose in order to maintain control. In several resistant cases control has been impossible. Patients treated with bretylium must thus continue under the irksome close supervision which has been required to achieve satisfactory control with other drugs.

It may be that combination of bretylium with a ganglion-blocking drug, each in relatively smaller dosage, and possibly also combined with chlorothiazide, will prove more effective; and our first attempts in this direction are fairly encouraging.

(2) *Instability.*—Fluctuations in blood-pressure have led to prolonged difficulty in stabilisation. We have observed considerable swings in pressure when recordings are made at hourly intervals through the day; so single readings in consulting-room or clinic may be very misleading. Dizziness and occasional syncope have been alarming alike to patients and their medical attendants. So far we have been lucky in avoiding disaster, but we are not surprised to learn that others have been less fortunate. The absorption studies reported from the Hammersmith Hospital provide a scientific basis for these clinical findings. It may be that with increasing experience our technique of administration will improve, but low and variable absorption and relative lack of warning symptoms still constitute a major problem.

(3) *Side-effects.*—It can be said at the outset that these have been less frequent and less severe than with any other effective drug used in the treatment of hypertension over the past ten years.

Treatment has had to be abandoned on only two occasions, but, as can be seen from the following figures, the incidence of side-effects is high. Some are of considerable interest and merit discussion.

Side-effects in 40 Patients

Dizziness (not due to postural hypotension)	15	Nasal congestion	6
Chest constriction and paræsthesiæ	9	Headache	6
Parotid pain	9	Weakness	6
Diarrhœa	8	Salivation	3
Frequency	8	Sweating	3
		Dyspnœa	3
		Tinnitus	3

Dizziness may, of course, be due to postural hypotension, but has also been a subjective complaint in many in whom the pressure is still high. Since this symptom has not been a feature of treatment with other hypotensive drugs it must presumably be due to bretylium.

A sense of *constriction or paræsthesiæ* across the chest and down the arms has been another unexplained complaint which in some ways simulates angina pectoris but bears no relation to effort and is not accompanied by electrocardiographic changes. Possibly both this symptom and dizziness are due to sensory disturbances in the distribution of the cervical and upper dorsal sympathetic nerves.

Parotid pain may be severe and recur at the beginning of each meal or from sucking a sweet. It is not always associated with excessive salivation.

Diarrhœa is seldom troublesome, but in some patients it recurs with every increase in dose.

Frequency of micturition has been reported by patients of both sexes and is usually nocturnal. Diarrhœa and frequency may perhaps be attributed to a swing from parasympathetic blockade to parasympathetic " release " and sympathetic blockade.

Nasal stuffiness tends to persist but has not been disabling.

Headache is presumably due to vasodilatation.

Weakness is an ill-defined sensation and we have no evidence that it is due to actual muscular paresis.

There is some suggestive evidence that dyspnœa may be due to pulmonary œdema.

In general, side-effects have been mild, and some of the ill-defined complaints may be due to autonomic imbalance, but further investigation is required for their elucidation.

We thought that a useful purpose might be served by grading our results in a similar manner to that described in the paper by Professor McMichael and his colleagues. On this basis, as far as experience goes, we have obtained 50% of good results compared with their 60%. We have been accustomed, however, to using somewhat different standards for grading results in that a good response has been claimed only if the standing diastolic pressure could be maintained at normal or near normal levels (and not simply a reduction of the diastolic pressure by, say, 20 mm. Hg). By these criteria our proportion of satisfactory results with bretylium is lower.

Experience to date would therefore seem to indicate, as the Hammersmith workers suggest, that bretylium, for all its advantages, is probably less reliable than the ganglion-blocking drugs at present available; but experience is still limited and it is too early to make a strict comparison.

From these observations it is clear that no highroad has opened before the hypertensive patient, and for this reason we feel strongly that a new compound such as this should not be widely recommended before the results of adequate clinical trials have been published, on a basis of which all clinicians can draw their own conclusions. To do so is to invite difficulty, disappointment, and even disaster, since patients who are inadequately controlled may sustain severe postural hypotension and may even lose their lives from syncope, cerebrovascular accident, or myocardial infarction. Without preliminary hospital assessment some will receive unnecessary treatment and others with serious hypertensive disease will receive inadequate treatment. If patients living at a distance are discharged from hospital, it is far better that treatment should be continued under the supervision of a clinic or a physician thoroughly familiar with all aspects and difficulties of the treatment of hypertension, and where this is not possible it is better not to use relatively untried remedies.

Those who intend to use such drugs should be aware of the difficulties, dangers, and possible side-effects, and these facts should be stressed in all recommendations for treatment and in particular by the advertisers.

We have no doubt that after 10 years of ganglion-blocking drugs a new era is beginning in the treatment of hypertension, and doubtless this is one of the first of a new series of very promising preparations. Its chemical, pharmacological, hæmodynamic, and therapeutic effects are of very great interest and importance, and much credit is due to the research-workers responsible for its production; but it would be a profound mistake to imagine that the treatment of hypertension has been greatly simplified. In a way it has become more complex, because now new possibilities exist and the relatively experienced physician may be tempted to dabble with mild cases or persist too long in resistant severe cases. Before these drugs are widely used in practice far more experience should accumulate.

RICHARD TURNER
CLIFTON LOWTHER.

Edinburgh.

THE MARRIED MENTAL DEFECTIVE

SIR,—The follow-up study of married mental defectives in Sheffield, outlined by Dr. Shaw and Dr. Wright (Jan. 30), is most interesting, but disturbing.

Of the original 242 defectives, 45 are untraced; the majority of the remainder show an I.Q. distribution of between 50 and 69, a much higher birth-rate, infant-mortality rate, unemployment-rate, criminal record, and percentage of their children attending special schools than applies to the community at large.

Live births were 50% greater than the norm for women married at the same age and for the same length of time; infant-mortality rates, such as are known, were very much greater than for the community at large (26 infants known to have died); a third of the families with one or more children were known to the National Society for the Prevention of Cruelty to Children or under the care of the children's department, and the percentage of their children at special schools seventeen times higher than for the Sheffield school population as a whole.

Surely this *is* a clear-cut picture which demands some action other than the patience and forbearance and tolerance that the authors ask of other people in the same community? It is good to know that some of the defectives are leading normal lives. Are the others offered birth-control advice, or indeed sterilisation . . . and, if not, why not?

The laws relating to sterilisation in this country are obscure, but most people agree that the subnormal couples with a large family and incapable of dealing with birth-control measures are eligible, if capable of giving consent, as also are those with subnormal mentality with a known eugenic chance of inheritance. A high proportion of these families would seem to come into one or other of these categories. Surely, if they are considered capable of making decisions to get married and have children, they must equally be capable of taking decisions about sterilisation?

Compulsory eugenic sterilisation is, of course, not legal, but I find it difficult to believe that some, at least, of such couples, faced with the difficulties that this survey brings to light, would be unwilling to accept birth-control advice or sterilisation, if offered it.

London, N.W.1. ELEANOR MEARS.

PERTHES' DISEASE

SIR,—Your annotation last week on Perthes' disease is welcome, for it may call the attention of the medical profession beyond the restricted field of orthopædic surgeons towards this condition. Nevertheless, it does not mention a factor which may be of decisive importance in its ætiology—namely, that with individual and very probably racial variations, from the age of three to eight years the blood-supply of the proximal femoral epiphysis comes through the small group of lateral epiphyseal vessels without complementary supply from the round ligament or the metaphyseal vessels. This precarious system of blood-flow occurs, at least in the white child, until or before the age of eight years, while the children of African origin seem to preserve the fœtel circulation through the vessels of the ligamentum teres throughout childhood. Perhaps for this reason the Negro child appears to be immune to Perthes', or at least seems to be only exceptionally affected by it as compared with the European child.

As to the late consequences of Perthes' disease, in our analysis of over 125 cases we found that, as was to be expected, the only hips suffering from osteoarthritis in adulthood were those left by the early osteochondritis either misshaped or incongruent, or both. Thus, to prevent this possible calamity all precautions should be taken; among them, for the moment, bed recumbency during the period when the dead bone is replaced by soft, malleable new cartilage.

Nuffield Orthopædic Centre, Oxford. J. TRUETA.

CONTROL OF ANTICOAGULANT THERAPY

SIR,—The isolated sentence from our paper quoted by Professor Quick (Jan. 30) was meant in no way to detract from the basic physiological and practical diagnostic merits of the one-stage prothrombin-time technique. Still less could the sentence be construed as having any relevance to very different procedures like the thromboplastin generation test; the reasons for this cannot be given here, and no-one is more aware of them than Professor Quick. Indeed, the offending sentence has little meaning at all except within the context of anticoagulant therapy, which was the subject of our discussion.

The acknowledged virtues of Professor Quick's test, described by us as a landmark in the physiology of coagulation, are too great to be seriously impugned by the recognition of certain limitations within a given context. We specified and discussed the shortcomings we had in mind: they refer only to the use of the unmodified test in the routine control of anticoagulant therapy and are not mentioned in Professor Quick's letter, while he appears to rebuke us for criticisms we did not make. Surely he would not deny that unduly severe depression of true prothrombin and of factor IX can exist unrevealed by the one-stage test, and that bleeding does occur, though not often, when the clotting-time is within the therapeutic range. With plasma from patients under coumarin treatment (though more doubtfully in the case of isolated deficiencies) thrombotest is sensitive to variations in all four factors concerned. Unlike the one-stage test it has been tailored to meet the requirements of anticoagulant control, successfully so far as we can judge though more extended trial should settle this question.

One at least of Professor Quick's shafts—the glass-lined blood-vessels—was misfired, whether through misreading on his part or obscure writing on ours. We did not list insensitivity to the contact factor as a shortcoming of the Quick test, but sensitivity to it as a disadvantage of thrombotest.

Dr. Laurie is quite right in his statement (Jan. 23) of a much higher price for commercially supplied thrombotest reagent than the 4*d.* per test suggested in our paper (Dec. 26). This over-modest figure was innocently based on the value given for Customs purposes added to the duty charged—amounting in fact to 3½*d.* per test. We have since confirmed that the present cost per test of purchased reagent would be about 1*s.* 6*d.*, a price at which thrombotest, with all its technical virtues, would be unjustifiably dear for routine use in this country. It is doubtful whether any test costing more than 6*d.* for the reagent is worth while. A way of reducing the cost of thrombotest may be found—e.g., by using smaller volumes of blood and reagent, though so far our own experience with small volumes is not encouraging.

Department of Pharmacology and Therapeutics, Queen's College, Dundee. W. WALKER J. M. MATTHEWS.

THE SIGN OF BABINSKI

SIR,—In your leading article last week, reviewing the history and significance of this sign—of which Walshe has written[1] that "there is perhaps no more important physical sign in clinical neurology"—you fail to mention the curious but surely relevant fact that the Babinski reflex can be demonstrated in many hypnotic subjects when regressed to infancy. This is difficult to explain on the information available, unless there were some evidence of concurrent neurological or biochemical changes as a result of regression or the hypnotic trance itself. But there is to date no such evidence.

This phenomenon was investigated in America by Gidro-Frank and Buch,[2] who found that the change of response from plantar to extensor was accompanied by what they described as a reversal of the flexor-extensor chronaxie ratio, which, it was claimed, is normally the case in the truly infantile condition. Later True and Stephenson[3] confirmed the presence of this reflex in subjects regressed to infancy, but showed that the E.E.G. was nevertheless of the adult form. However, the genuineness of the phenomenon is still debated on both sides of the Atlantic and is, indeed, very difficult to prove, although most deep-trance hypnotic subjects will produce the response. Gidro-Frank and Buch claimed that their subjects had no knowledge of the reflex or the intention of the investigators, but for my part I have not yet discovered a suitable subject of whom it could be said with certainty that there was no such knowledge. But one subject, a student nurse in her first year, when deliberately misinformed and told with authority (as a temporary, experimental measure) that she had got it muddled and that the infantile response was flexor, nevertheless provided a first-class demonstration of the extensor reaction when regressed to the age of five months.

Lower Beeding, Horsham, Sussex. STEPHEN BLACK.

SIR,—Your interesting editorial mentions instances of a temporary Babinski sign, rapidly reverting to normal. A more gradual reversion can also occur in cerebral vascular disease.

Examples of this were seen when 125 patients with hemiplegia, following cerebral vascular accident, were examined at fortnightly intervals for six months. Some 53 of these cases showed an up-going toe on both sides: the remaining 72 had a positive sign on one side only. Out of these 178 responses, no less than 41 (25%) had returned to normal within six months. Such reversion took less than two months in 8 patients; from two to four months in 14 patients; and more than four months in 17 patients. 1 patient with bilateral Babinski signs showed reversion in one week on the left side and three months on the right side.

Queen's Hospital, Croydon. TREVOR H. HOWELL.

1. Walshe, F. M. R. Diseases of the Nervous System. Edinburgh, 1940.
2. Gidro-Frank, K., Buch, M. K. B. *J. nerv. ment. Dis.* 1948, **107**, 443.
3. True, R. M., Stephenson, C. W. *Personality*, 1951, **1**, 252.

CASE-FATALITY IN TEACHING AND NON-TEACHING HOSPITALS

SIR,—We should like to amplify the last paragraph of Mr. Ellison Nash's letter of Jan. 23.

No doubt in the larger non-teaching hospitals all the night emergency anæsthetics are administered by junior staff; but this is not the case in many smaller hospitals. Most provincial hospitals of 300-400 beds have establishment for only one resident anæsthetist—if they can find one. On his nights off duty, usually six out of each fourteen, and for the first few months of each new appointment, every night anæsthetic is administered by a consultant.

In one such hospital of 300 beds, in 1958 the resident anæsthetist gave 342 anæsthetics for emergencies of all kinds, and the consultants, with 16 nominal sessions, gave or personally supervised 322. Some of these were when the consultants concerned were already in the hospital; considerably more than half entailed special visits outside their normal hospital hours.

These figures are not exceptional, but probably represent the average for such hospitals.

The quality of work must surely deteriorate under such conditions, where the individual is frequently tired before the start of a fresh routine day, whatever his actual status. With advancing years recovery from a night's work is apt to be slower and less complete.

ERIC FOWLER
RUSSELL M. DAVIES.

Tunbridge Wells.

EFFECT OF BEER ON BLOOD FIBRINOLYTIC ACTIVITY

SIR,—Dr. Ingram (Feb. 6) cannot have read our paper very carefully. We did not, as he suggests, compare the effect of a large volume (10–40 oz.) of an alcoholic drink with that of a small volume (2 oz.) on blood fibrinolytic activity. It is stated both in the text and in the heading of table III that the 2 oz. of whisky were taken in a pint of water. A separate statement to this effect is not made about the results quoted in table I, and I think that it should have been, but this hardly justifies Dr. Ingram's sweeping misquotation.

Since he asks whether the lysis-time is prolonged by swallowing 10–40 oz. of water, I can tell him from other experiments that it is not.

Gloucestershire Royal Hospital, Gloucester. G. R. FEARNLEY.

AUTOTRANSFUSION IN RUPTURED ECTOPIC GESTATION

SIR,—Professor Chassar Moir in his letter of Jan. 2 is the only contributor to the correspondence following Mr. Azie's letter (Dec. 12) who has mentioned the age of the blood from the peritoneal cavity, and he was not precise.

Hamilton Bailey's *Emergency Surgery* counsels hesitation when the hæmorrhage is more than 10 hours old, and an earlier edition I believe gave 8 hours as a definite contraindication.

In my experience in West Africa cases almost never presented as early as this, and in the several dozen cases I had to treat I never attempted autotransfusion. In this course I was influenced by Hamilton Bailey, and by experience and teaching on first arrival abroad, because these cases did so well with immediate laparotomy alone, reviving almost dramatically from the time the bleeding point was clamped. One gained the impression that if they had a pulse when they had been anæsthetised and reached the table, they would survive.

I am not decrying the practice of transfusing freshly shed blood, but it seems an important point to know how late it may safely be used, for the guidance of those whose work lies in those areas where the average time before a ruptured ectopic is seen is probably well over 12 hours. I have often wondered whether the use of blood too long shed has not contributed to an unsuccessful result, the advice to autotransfuse having been followed as long as the blood was fluid.

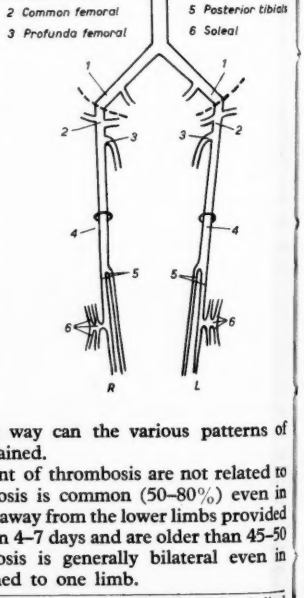
London, N.W.1. H. DE GLANVILLE.

ÆTIOLOGY AND PATHOGENESIS OF DEEP VEIN THROMBOSIS

SIR,—In his letter of Jan. 16, Professor Quick states that *impaired circulation* is rarely, if ever, the primary cause of intravascular clotting and postulates that deep vein thrombosis is initiated by *local injury* of a vessel wall. I take the opposite view, that a reduced venous flow is essential and that local injury is rarely the cause. Of course, he states that the secondary added thrombosis is dependent on the locally formed thrombin not being swept away by a normal venous flow and thus slowing of the venous stream would explain propagation of thrombi.

Local trauma cannot explain venous thrombosis in patients without injury (medical cases) or in those with injury away from the lower limbs; nor the multiple and varied distribution of the thrombi found at necropsy. Routine dissection of the deep veins of the whole lower venous tree in patients dying after various injuries has shown that venous thrombosis is very common; that the frequency is related to advancing age and survival period (bed rest); that the nature of injury has little direct influence; and that a large variety of patterns of thrombosis occurs.[1 2]

These patterns indicate that thrombosis *begins* at one or more of several independent sites. Six main primary sites are recognised (see accompanying figure): (1) the iliac vein, generally the external iliac vein just above the inguinal ligament; (2) the common femoral vein including the mouths of the medial and lateral circumflex veins; (3) the termination of the deep femoral vein, usually at a valve cusp guarding the ostium; (4) the popliteal vein near the adductor ring; (5) the posterior tibial vein; and (6) the intramuscular veins of the calf, particularly the soleal veins. Thrombosis at one site is independent of thrombosis elsewhere and may then extend by forward propagation or retrogradely after occlusion of the lumen. Only in this way can the various patterns of thrombosis found be explained.



The frequency and extent of thrombosis are not related to the site of injury. Thrombosis is common (50–80%) even in patients dying after injuries away from the lower limbs provided that they survive longer than 4–7 days and are older than 45–50 years. Moreover, thrombosis is generally bilateral even in patients with injury confined to one limb.

1. Sevitt, S. *in* Modern Trends in Accident Surgery and Medicine (edited by R. Clarke, F. G. Badger, and S. Sevitt); p. 247. London, 1959.
2. Sevitt, S., Gallagher, N. G. (in the press).

The multiplicity of primary foci and the lack of relationship of thrombosis to the site or side of injury cannot be explained by local trauma, and this is supported by histological observations which show that recent thrombi are laid down on normal endothelium.

That advancing age and duration of bed rest (survival period) are the most important factors predisposing to thrombosis supports the old contention that venous stasis plays a major ætiological role. This is also supported by abundant evidence that the blood-flow through the lower limbs is greatly slowed during bed rest.

Emptying of veins depends on muscle contraction, and lack of this, particularly in the elderly put to bed for any reason, will allow the blood in the lower limbs to become stagnant. Thus, anatomy and the dynamics of blood-flow decide where thrombi *begin* to form. Thrombosis occurs in the soleal veins because they become distended with stagnant blood in the horizontal position of bed rest and, as shown by Gibbs [3], because they form a number of inverted intramuscular arcades which increase in number and lumen diameter with advancing age. Thrombosis of the posterior tibial veins is possibly encouraged by the relationship of the vein to the upper edge of the soleus muscle; whilst the deep intramuscular location of the profunda femoris vein and pressure from the overlying adductor muscles help to slow its venous stream. Further, the inguinal ligament facilitates thrombosis in the common femoral vein because it may compress the vein when the thigh is flexed on the trunk, as in Fowler's position. Eddying of the stagnant blood-flow with consequent local silting of platelets and leucocytes on to endothelium probably plays a part in initiating thrombosis at least in the thigh and pelvic veins. Eddying and silting is likely to occur at valves and mouths of vein junctions at the termination of the profunda femoris, medial and lateral circumflex veins, and other tributaries of the common femoral vein. Above the inguinal ligament eddying and silting may initiate thrombosis in the external iliac vein because, when the body is horizontal, there is an acute weir-like change in direction of the slowed column of blood. In short, the common denominator of venous thrombosis is venous stasis; and, in addition to venous anatomy, which determines eddying, silting, and primary location of thrombi, the major roles are played by age, immobility, and above all bed rest. Injury per se rarely, if ever, plays an ætiological role.

Birmingham Accident Hospital. S. SEVITT.

BREECH PRESENTATION AND DELIVERY

SIR,—It would be a pity if external version were not to be attempted. The breech presentation is uncomfortable for the patient, and rightly or wrongly the expectant mother is nearly always apprehensive about it. Before anyone attempts version, however, he or she must clearly understand that there are two kinds of breech, " a cylinder within a cylinder, and a sphere within a sphere ". The former will not turn and can only very rarely be turned; the latter will probably turn themselves (but not certainly). They can, however, be turned, so why not? Vigorous attempts to turn the first type in the antenatal clinic are to be condemned and attempts under anæsthesia should certainly be abolished. Anyone who has had a disaster with version and has proved himself "accident-prone " should give it up.

The only exceptions I make are (1) if a woman is to be induced under anæsthesia then I would try a version first; (2) occasionally conditions are encountered which would be suitable if the patient could cooperate, but she won't.

What is much more serious is the steadily increasing cæsarean-section rate: in one hospital over half of the breeches were section in one year. By surgical induction the size of the baby can be controlled. In this way dystocia will be avoided; and we must all admit that dystocia in the breech is more troublesome than in the cephalic presentation. By a wider use of surgical induction, the rate of cæsarean section with all its potential dangers can be kept within responsible limits.

London, W.1. C. K. VARTAN.

THE ABNORMAL APPENDIX

SIR,—May I criticise Mr. Jewers' reasons (Dec. 26) for preferring a paramedian incision?

Firstly I disagree about the ease of approaching the appendix, especially the retrocæcal variety: in most cases the appendix can be removed easily through a gridiron incision. If the skin incision is made obliquely transverse in a natural skin crease following Langer's lines the incision can readily be extended laterally or medially. In dealing with a retrocæcal appendix, which more often lies towards the outer side of the ascending colon, I make my incision rather higher than usual and of adequate length, and have rarely found it necessary to use retractors, provided a good anæsthetic is given, which is most important. On the other hand, removing a similarly positioned appendix via a paramedian incision has always appeared difficult to me. Even when the tip of the appendix is lying towards the midline the base may still be found well out in the right iliac fossa and appendicectomy is still carried out more easily by the more direct approach of a gridiron incision.

Secondly, I consider the routine use of a paramedian incision, in case one's diagnosis is wrong, is to be deprecated, as it must encourage an attitude of mind whereby any case of abdominal pain is subjected to an exploratory laparotomy. I know it is often said that it is far better to take out a normal appendix than to miss a pathological one, but I have a feeling that too many patients are subjected to a laparotomy for abdominal pain and a normal appendix removed to justify this procedure. Even though the risk to life is minimal, it is never non-existent, and in addition to the risk of an anæsthetic death, there is that of intestinal obstruction at a later date from adhesions, and this is greater after a paramedian incision than after a gridiron.

It is preferable to observe the patient for a time if the indication for operation is not clear rather than submit a person to a rushed operation, for it will often be found to be unnecessary. In a series of 324 patients admitted to hospital as emergencies with abdominal pain and mostly seen by me, operation was performed for acute appendicitis in 158, conservative treatment for acute appendicitis was instituted in 21, and 59 cases of abdominal pain in which no accurate diagnosis was made initially were observed. In many of this last group no final diagnosis was reached. There were no deaths in any of these groups. Thus, a fairly high proportion of patients admitted as acute abdominal emergencies are found to have very little wrong with them, this applying particularly to the younger female group.

Conversely, as Mr. Jewers has pointed out, the symptoms and signs in the elderly are singularly lacking, but early diagnosis and operation is as imperative as in the very young. I have operated on a number of people over 75, including a few in the 80s, and have found that localisation of the infection is remarkably poor, especially in the obese. Severe peritonitis may be present with a normal pulse and temperature and only minimal signs in the abdomen, but invariably there is localised tenderness, however slight, over the appendix. In fact, I would go so far as to say that in any case of suspected acute appendicitis unless this tenderness is present I would question the diagnosis. Occasionally, of course, one is sure of some intra-abdominal mischief, but the exact diagnosis is obscure, and in these cases I quite agree with the use of a paramedian incision; but as a rule the commonest conditions with which acute appendicitis may be confused lie in the lower abdomen, and these can be dealt with efficiently by extending the gridiron incision medially and dividing the right rectus muscle transversely. The wound heals quickly and soundly.

Lastly, citing a low incidence of hernia after a paramedian

3. Gibbs, N. M. *Brit. J. Surg.* 1951, **45**, 209.

incision as an argument for adopting this approach is surely contrary to general opinion. An incisional hernia after such an incision is not infrequent, whereas I have seen a similar hernia after a gridiron incision once only. Regrettably, this was one of my own cases, but the patient was obese, and developed a severe wound infection. Fortunately, the repair of this was easy. But perhaps the fact that there is a greater incidence of right inguinal hernia in those having had an appendicectomy is what is implied.

Let me say that I found much of Mr. Jewers' paper excellent—and in particular the remarks on the use of antibiotics were most relevant. Too often a course of these drugs is started immediately appendicitis comes to mind, even when the infection is mild or non-existent. In the late case treated conservatively a long course of antibiotics is not without danger.

I remember well a man who had been ill for three weeks before admission being given prolonged chemotherapy, and at operation several months later I removed his appendix and drained a chronic encysted pelvic abscess. Postoperative obstruction developed, requiring further operation, from which he subsequently died.

My findings regarding the position of the appendix also confirm what Mr. Jewers says. The figure usually quoted of 0·5% [1 2] for the retro-ileal position has always seemed too low, while that of 21% [2] or 32% [1] for the pelvic appendix too high. Although I have not exact figures available, I have the impression that in my experience the retro-ileal occurs in 5% of cases at least. Probably the percentage of pelvic appendices mentioned is elevated by including many cases of subcæcal ones. I would not class an appendix as of the pelvic variety unless a part of it is definitely hanging over the pelvic brim. On the other hand, I would consider the high retrocæcal appendix due to a maldescended cæcum comparatively rare, whereas that with the cæcum in a relatively normal position is common, the tip of the appendix being found at varying heights behind the ascending colon to as far as the hepatic flexure. These usually require removal by the retrograde method, since they are buried in the retrocolic tissues.

Grove Park Hospital,
London, S.E.12. R. F. BOLAM.

TREATMENT OF INFECTIONS IN HOSPITAL

SIR,—Your annotation of Jan. 16 discussed the report of Finland et. al. on the changing pattern of infections. Once again the seriousness of staphylococcal infections was demonstrated.

That the old enemy, the hæmolytic streptococcus, is not yet beaten has been suggested by the rather disturbing increase in the isolation of this organism from the throats of children in this area. Not only has there been an epidemic of β-hæmolytic streptococcal throat infection in a large school, but also this organism has been isolated from more than a quarter of the throat swabs taken in one children's ward during the past year.

During the same period, the number of cases of acute rheumatism and acute glomerulonephritis seemed to be on the increase, so an analysis of the number of medical (as opposed to surgical) patients admitted to three children's wards during the past five years has been made. Practically all sick children from this part of the Black Country are admitted to one of these three units. All were fresh cases, and subsequent admissions for the same disease have been excluded.

Year	Total admissions	Acute rheumatism	Acute nephritis
1955	945	8 (0·85%)	11 (1·16%)
1956	1014	14 (1·38%)	12 (1·18%)
1957	1054	5 (0·47%)	11 (1·04%)
1958	1095	6 (0·55%)	6 (0·55%)
1959	1169	38 (3·26%)	20 (1·7%)

1. Aird, I. A Companion in Surgical Studies; p. 856. Edinburgh, 1957.
2. Bailey, H., Love, M. A Short Practice of Surgery; p. 587. London, 1959.

From these figures it will be seen that there has been a striking increase in the admission of patients with acute rheumatism and a definite, but less remarkable, rise in the number of children suffering from acute glomerulonephritis. One wonders whether this increase in the number of streptococcal infections is widespread. If so, is it because penicillin is less frequently used for throat infections at the present time? The broad-spectrum antibiotics which are so often prescribed at present are known to be less effective than penicillin against the streptococcus. Or can the commonly occurring penicillin-resistant *Staphylococcus aureus*, concomitantly present, produce enough penicillinase to render the streptococcus less sensitive to penicillin?

Wolverhampton. H. EVERLEY JONES.

THE COST OF DRUG TREATMENT

SIR,—Recent letters on this subject have made me break a resolution formed some time ago not to send another communication to the Press. My present breach is in spite of a conviction that any letter on the subject is only "a voice crying in the wilderness", but this letter is chiefly to endorse Sir Max Page's remark (Jan. 30) that "Savings on drug expenditure leave more money for hospital building, more doctors and more pay for them."

The subject has interested me more particularly since, as adviser on venereal diseases to the Ministry of Health, when, in 1920, I wanted to find money not then available for improvements in the V.D. service, I began to examine in detail the expenditure of the clinics, hoping that by checking waste the money already being expended could be used to better purpose. My investigation revealed waste, sometimes of the most idiotic kind, and prompted economies, *by persuasion*, that resulted in very substantial saving in the cost of the service. The experience during the decade 1920–30 convinced me that the average doctor does not give a thought to the question "is this drug in this form and this amount necessary?"

I described the methods by which economies were effected first in 1923 in an article entitled Economy in Drugs and Dressings, which was contributed, by invitation of Dr. F. N. K. (later Sir Frederick) Menzies, to the 5th annual report of the Order of St. John and the British Red Cross Society on the Voluntary Hospitals in Great Britain; and next in 1951 in a letter to *The Spectator* (Jan. 19, p. 79) to support an article by Dr. M. E. Lampard, published a fortnight previously in the same periodical, under the title Doctors and Drugs, in which he exclaimed at the waste that was then prevalent. I ended that letter with the following remarks: "If anyone reading Dr. Lampard's article and this letter is tempted to embark on economies in his branch of the N.H.S., he should not expect thanks. I should like to meet anyone who has been thanked for saving public money."

I learnt the importance of economy in drugs quite early in life, being a son of a practitioner who dispensed his own prescriptions. Later, as assistant to a country practitioner, I put my knowledge to some use in frequent gentle reproofs of my boss for the cost of his mixtures. Still later, in India, when one of my duties was charge of a cantonment hospital, for native civilians, I had to work to a budget which did not err on the side of extravagance and I had to find the money for new instruments, such as cataract knives, by watching every anna. It was a very useful experience and it prompts me to suggest that if doctors had to work to budgets in respect of drugs, dressings, and instruments—budgets *framed by people with practical experience*—we should see the taxpayers' money used to better purpose in that branch than at

present. I know because I have tried it and it has worked. Often in my visits to V.D. clinics I was asked by a medical officer if he could have such and such a rather expensive instrument or apparatus, and from information as to the details of his expenditure in his clinic, read in the light of my experience in my own clinic, I was able to tell him how to save enough to buy the tool he wanted.

London, S.W.1. L. W. HARRISON.

SIR,—Dr. Miller and Dr. Smith (Jan. 2) make the retail pharmacist the scapegoat for the rising drug bill. As a retail pharmacist and one-time hospital chief pharmacist, may I reply to the criticism of excessive distributive costs which suggests that retail pharmacists are overpaid for their services.

The argument rests on the disparity between the basic cost of drugs and the final cost which is determined by the profit or fee paid to the pharmacist. There is, however, no logical connection between the basic cost and fees paid for distribution. Phenobarbitone is cheap, but why should the pharmacist's fee be related to the cost of phenobarbitone? The cost of the general medical practitioner's share in the distribution of phenobarbitone is at least equal to that of the pharmacist, but no-one would suggest that medical fees should be assessed in this way. The pharmacist's fee is related to the cost of providing centres for distribution of drugs as well as for the actual dispensing services. In relation to the actual costs of providing the service, the pharmacist is not overpaid—even if the cost of distribution is one-third of the drug bill. Not many pharmacists earn more than £1000 per annum from dispensing.

The comparison with hospital costs is most misleading—it is very difficult in hospital costing to relate costs to any unit of work. The hospital pharmacist makes many economies for the management committee by judicious buying, but comparative costs would have to include a proportion of maintenance that your contributors ignore.

It is not generally recognised what a good service the patient gets from the retail pharmacist, who daily has to obtain quickly new proprietaries and who cannot substitute chemical "equivalents" as is done in the hospitals. It is, of course, quite true that a more rational distribution of drugs and of medical services could be devised, but costs would still have to be related to many other factors apart from basic prices of drugs.

London, E.C.1. W. C. KING.

SKIN CHANGES IN HYPOCALCÆMIA

SIR,—The paper by Professor Dent and Dr. Garretts (Jan. 16) leads me to record a further case confirming their findings, but I also wish to point out that the presenting feature in this patient was his mental state.

A 64-year-old man was recently admitted to hospital suffering from quite severe depression, retardation, and lack of initiative. He had widespread scaling of the skin, especially on the arms. There was bluish-red erythema in the folds of the groins with some oozing. He had generalised muscular hypotonia and passed bulky stools. The following tests were carried out:

Blood-picture showed anæmia with some macrocytosis.

Glucose-tolerance test showed sugar levels of 86, 81, 111, 113, and 106 mg. per 100 ml. at half-hourly intervals. No glycosuria.

Serum-protein 6·1 g. (albumin 3·8 g., globulin 2·3 g.) per 100 ml. Serum-calcium 6·7 mg., phosphorus 3·0 mg., bilirubin (direct negative) 0·5 mg., thymol turbidity 2 units, zinc turbidity 5 units, alkaline-phosphatase 30 King-Armstrong units per 100 ml.

Faeces: 72-hours total fat 108 g. (80% total solids); split fat 93 g. (68% total fat).

Almost certainly a case of idiopathic steatorrhœa, he is being treated, with improvement, by folic acid, 'Parentrovite', and imipramine.

The skin lesions have been recurrent for sixteen years. His psychiatric history reveals that he had electroconvulsion therapy for depression in two other hospitals in 1952 and 1954. He was a patient here in 1955 and last year, on both occasions in a state of hypomania. In 1955 his serum-calcium was 9·5 mg. per 100 ml., and there was only slight scaling of the arms.

Thus his "skin health" seems associated with his blood-calcium level. An episode of depression accompanied the hypocalcæmia, and as 2 of Professor Dent and Dr. Garretts' 4 cases showed states of acute anxiety and suicide-level depression, I think it is essential to emphasise the dangers, from a psychiatric point of view, in this condition.

I wish to thank Dr. J. A. S. Mulligan for permission to publish this case.

St. Luke's Hospital, Armagh. W. A. GORDON MACCALLUM.

SIR,—We are interested to note the point raised last week by Dr. Brian Russell, whose patient with erythrodermia did not show a correlation between the rash and the hypocalcæmia. We are not surprised about this as we intended to state in our paper that it is only in certain patients that such a correlation can be noted. The vast majority of patients with hypocalcæmia do not get any sort of skin trouble, and the majority with various forms of skin trouble do not have hypocalcæmia. The point of our paper was only to state that sometimes there was such a correlation between hypocalcæmia and skin disease and that in such cases it was important to deal with it as there was no other treatment. We are sorry if it was not clear enough in our paper.

University College Hospital Medical School, London, W.C.1. C. E. DENT
M. GARRETTS.

INFANTILE STRUCTURAL SCOLIOSIS

SIR,—Your annotation of Jan. 30 is a curious one. It says "there is much to be gained by the further study of the natural history of severe deformities, and until this is understood it is wrong to claim that any particular treatment has been successful." I would find this easier to understand if I knew what methods and what claims were being referred to. I do not appear in the list of references, but as far as I know I am the only surgeon to suggest[1] that the terrible deformity of "idiopathic scoliosis" starts in utero, and can be detected in early infancy and cured at that stage by splinting and physiotherapy. The present teaching of orthopædic surgeons appears to be that because some cases get better spontaneously therefore none at all should be treated.

I do not know what they would reply to the mother of a child with "severe and progressive scoliosis" who says, as several have said to me, "I kept telling them that the baby's spine was crooked, and they just laughed at me."

I have aroused considerable resentment by suggesting that treatment is absent because there is no classical splint to reverse the curve of the spine, any more than there is one to reverse the commonest of all elements in deformities of the feet—that of equinus.

London, W.1. DENIS BROWNE.

*** The prime object of our leaders and annotations is to note and discuss new work: we hardly ever aim at a comprehensive review and an exhaustive list of references. In this annotation we were concerned with the recently published work of James et al. and not with all the possible ætiological factors that might combine to produce

1. Browne, D. *Proc. R. Soc. Med.* 1956, **49**, 395.

the condition. We thus excuse ourselves for feeling no need to recall Mr. Denis Browne's considerable and well-known contributions to this subject. We still affirm that the best treatment is usually based on a knowledge of what causes natural resolution. It was never our intention to suggest that *no* deformities should be treated. —ED. L.

ANTI-SMOKING CAMPAIGN

SIR,—The article last week on the efficacy of an anti-smoking campaign is full of interest. It is not surprising that it failed to diminish the amount of smoking, because " drug addicts " cannot be cured by exhortation, the only remedy is to make a harmless cigarette that people will smoke.

It is interesting that after the campaign there was evidence that people realised to a greater extent the harm done to bronchitic people, but it did *not* increase the awareness of the connection between smoking and cancer of the lung. The authors are undoubtedly correct in saying that this is a form of " emotional blockage " due to fear of cancer " long nurtured by a conspiracy of silence ". This psychological problem can best be solved by personal conversations between a lay person and a member of the nursing profession—i.e., health visitors, district nurses, and midwives. If local authorities would spend half the time, money, and energy at present spent on anti-smoking campaigns in arranging for their nurses to talk to the public about the symptoms of the " accessible cancers " they would get immediate results.

Oxford. MALCOLM DONALDSON.

CASUALTIES AND CASUALS

SIR,—Two points may influence Dr. Fry's conclusions (Jan. 16) and Dr. Doyne Bell's comments upon them (Jan. 30).

Both doctors are Londoners. London has a large " floating population " which increases the number of " casuals "—travellers, troupers, workmen on location, and so on. They have no family doctor near them because they have no family life. They have a right, one might think, to look to the nearest hospital when they are in need. All casualty departments have a few of these patients, but London has a lot.

Secondly, the little clinics doing family doctor's work which have developed in casualty departments grow by what they feed on. The more they are treated, the more they come. Dr. Fry seems to disapprove of them, and so do I. Nevertheless, if I remember rightly many young casualty officers did not discourage these opportunities to try their wings, from the shelter of their hospitals, before launching out upon more serious flights. If the hospitals themselves disapprove nowadays, I do not think they did so always.

My first point is that this work should not entirely disappear, and my second that to a very large extent the volume of it depends upon what you make it. A consistent policy about what one's own casualty department considers it should treat, and what can be treated equally well or better in the doctor's surgery, can of itself determine in which way the work develops. I have misgivings about national decisions about what casualty departments as a whole should or should not do.

Dr. Doyne Bell refers to the " consultant who is ultimately responsible " and to the difficulty of deciding which particular specialist would be the most appropriate. I often wonder what this ultimate responsibility means, and suspect its interpretation in many minds would be " carrying the can ". Strict conformity with the limits each specialty sets for itself could reduce casualty department work to a farce, and I detect signs that the farce is likely to begin before long. The casualty department cuts across all specialties. Because it is very often concerned in emergencies and accidents *of all types* it would be a great mistake for it to be gathered into any particular sphere of specialist influence. In most hospitals, on the other hand, staffing problems make it impossible to share the work amongst all the different specialties concerned. The sooner we accept that the casualty department is part of the hospital as a whole, and that it should command the support of all the faculties, the better for the hospital service.

As a surgeon, I should like to agree with Dr. Doyne Bell that our casualty departments could be defined as accident, emergency, and dressing stations. I do agree that we could make many of them much more like his definition than they are. As a doctor, I see quite a number of cases outside his definition that I simply cannot send away.

Sunderland. T. G. LOWDEN.

NATURAL HISTORY OF CAVERNOUS HAEMANGIOMATA

SIR,—

" In Xanadu did Kubla Khan
A stately pleasure dome decree:
Where Alph, the sacred river, ran
Through caverns measureless to man
Down to a sunless sea "

According to the correspondence in your columns cavernous hæmangiomata appear to be measureless to man's judgment, but I believe the main body of opinion in the many letters gives the truth of the matter. So I would have left it, but I have been invoked as an authority and I am convinced that spontaneous resolution, usually in the first decade, is the rule, and I can recall seeing only three adults with lesions of this type. However, the obvious lesions, especially those on the face, cause much distress to the parents, and it is usually possible to hasten natural resolution by X-ray dosage well within the safety margin.

When parents wish for something to be done I prefer to use X-rays with a half-layer value of 1 mm., or not exceeding 1·5 mm., of aluminium with a dosage of 250r, repeated after a month's interval for three doses. Smaller lesions can sometimes be given 300r, and exceptionally four doses might be given. Within this range no erythematous reactions were observed nor any atrophic sequelæ. No irradiation was given in the vicinity of the thyroid glands. For many years treatment was not given to lesions which were hidden by clothing, and those all disappeared satisfactorily well within the first decade.

London, W.1. REGINALD T. BRAIN.

SIR,—I read Dr. Simpson's excellent article (Dec. 12) with great interest and I am in full agreement with all the supporters of the " wait and watch " school. My only excuse for this letter is to quote from the writings of an acute clinical observer of the pre-X-ray and pre-carbon-dioxide-snow era—Thomas Bateman. In the 6th edition of his book, *A Practical Synopsis of Cutaneous Diseases*, according to the arrangement of Dr. Willan, published in 1824, on p. 331 he writes of this group of nævi:

" Some of these excrescences are raised upon a neck or pedicle, while some are sessile upon a broad base. Some of them again, although vivid for some time after birth, gradually fade and disappear: some remain stationary through life, but commonly vary in intensity of colour at different seasons and under circumstances easily explained: and others begin to grow and extend, sometimes immediately after birth, and sometimes from incidental causes at a subsequent period, and from small beginnings become large and formidable bloody tumours, readily bursting, and pouring out impetuous and alarming hæmorrhages, which, if they do not prove suddenly fatal, materially injure the health by the frequent depletion of the system. Sometimes, however, after having increased to a certain degree, they cease to enlarge, and thenceforth continue stationary, or gradually diminish, till scarcely any vestige remains."

There is no doubt from this that Bateman was aware of the spontaneous resolution of these lesions. The graphic description of "impetuous and alarming hæmorrhages" tells of a course of events which nowadays must be extremely uncommon but may possibly account for the surgical emergencies of which Mr. Denis Browne writes.

I, along with many other dermatologists, would welcome the opportunity of seeing some of the adult patients with cavernous hæmangiomata whom Dr. Colin-Jones (Jan. 2) meets so frequently in Sussex. As Mr. McLaughlin states (Jan. 16), to treat or not to treat is still one of the most difficult questions in dealing with cosmetic problems.

Oxford. H. R. VICKERS.

INTRATHECAL PHENOL IN THE TREATMENT OF SPASTICITY

SIR,—I wonder whether an interested reader who has treated no patients by this technique and who has made no contribution to the subject can add a comment to the recent correspondence regarding the history of this method of treatment.

Dr. Maher's original work on the use of this technique in the treatment of pain, particularly in malignant conditions, is acknowledged by the writers concerned. So far, however, I have seen no reference to the fact that in the second of his papers (January 1957)[1] there is a brief but favourable mention of his use of this treatment in a case of hemiplegia with severe flexor spasms. This was, I believe, the case referred to by Dr. Liversedge in his letter of Jan. 2 in which improvement has been maintained over a period of three-and-a-half years.

I am drawing attention to this reference in the interest of accuracy.

Oldham. J. STARKIE.

DIAGNOSIS OF MULTIPLE PREGNANCIES

SIR,—In your annotation of Jan. 30 you make the remarkable claim that multiple pregnancy can be demonstrated by the electroencephalogram. The annotation would have little value did it not imply the maternal electroencephalogram!

It is, of course, well known that sensitive balanced recording amplifiers of the type used in electroencephalographs, when connected to electrodes placed on the abdomen of a pregnant patient, will record the R waves of the fœtal heart or hearts.[2] This technique is in general use in many obstetric hospitals and over 200 papers have been published on the subject in the past 40 years.

The time constants of the electroencephalograph type of amplifier are not ideal for the purpose and a greater degree of success can be achieved by following the design recommendations of Bell.[3] The maximum energy in the fœtal R wave occurs in about 0·02 second. An amplifier with a time constant of 0·02 second and restricted band-width will give success in almost every case. As you mention, around the 30th week of gestation recording is difficult; this is due to excess vernix caseosa.

Recent work [4] has shown that the presence of a fœtal QRS complex is not always a sign of life, for it may sometimes be obtained from a severely macerated fœtus.

In the diagnosis of multiple pregnancy it should be remembered that fœtal electrocardiography may indicate single pregnancy if one of twins is stillborn.

An advantage of using an E.E.G. machine for fœtal cardiography is that it will also read the electroencephalogram from the maternal abdominal surface and on occasions show slow waves of large amplitude. Such waves are characteristic of gross anoxia in the newborn and may indicate the same condition in the fœtus also.

1. *Lancet*, 1957, i, 16.
2. Smyth, C. N. *Lancet*, 1953, i, 1124.
3. Bell, G. H. *J. Obstet. Gynæc. Brit. Emp.* 1938, **45**, 802.
4. Smyth, C. N., Farrow, J. L. *Brit. med. J.* 1958, ii, 1005.

University College Obstetric Hospital, London, W.C.1. C. N. SMYTH.

HYPOTHERMIA FOR NEUROSURGERY DURING PREGNANCY

SIR,—The report [1] on hypothermia and hypotension in a pregnant woman was of particular interest to me.

On March 31, 1958, eight months prior to the admission of Wilson and Sedzimir's patient, a woman aged 34 years, who was twenty-four weeks pregnant, was sent to the neurosurgical unit of St. George's Hospital (Atkinson Morley's Hospital) after a cerebrovascular accident.

Examination revealed a normal fœtal heart, and neurological investigation showed that the patient had bled from a right parietal angioma.

The position and size of the tumour was such that it was decided to operate under hypothermia and in the sitting position (bolt upright)—as if for a posterior-fossa tumour. Mr. Wylie McKissock completely excised the tumour and the patient made an uneventful and successful recovery.

Following induction of hypothermia the fœtal heart-rate fell from a preoperative 180 to 120 per min. at 30°C; but always remained regular and returned to normal after the mother's body temperature had been restored.

The pregnancy came to full term and the child was delivered normally with the full cooperation of the mother. Both mother and child are doing well.

This case is to form part of a paper on a simplified technique for large-scale hypothermia for neurosurgery.

Cape Town. JACK LEVIN.

PREVENTION AND TREATMENT OF BEDSORES

SIR,—Dr. Roberts (Jan. 30) has drawn attention to a subject which deserves a very full study. 33 out of 250 patients (13·2%) treated in a geriatric unit during the past four months were found to have bedsores at the time of their admission. The stay in hospital of such patients is often prolonged (on average, it was 40 days as against 25½ days for those without bedsores). Moreover, the mortality is four times as great if pressure sores are present. The study of factors leading to the development of bedsores is therefore an important aspect of preventive medicine, and the interest of medical officers of health and district nurses in this matter is to be welcomed.

It is generally recognised that all patients who are nursed in bed—and especially the elderly—are exposed to the danger of pressure sores. The risk, however, varies considerably with different types of patient, and it is greatest for those whose general condition is poor. Because of this variation in risk the comparison of the value of different prophylactic procedures is difficult. In order that an assessment can be made more accurately we have been using a scoring system based on the patient's physical condition, his mental state, his activity, his ability to change position in bed unaided, and the degree of incontinence when this exists. The scoring can be carried out simply, and closely similar results are obtained by different observers. With this system possible scores are within the range of 5–20, and by making the score on admission to hospital and at weekly intervals the change in the patient's condition during the course of his illness can be assessed. The average score for patients who already had pressure sores was 11·0 on admission, and of those who developed pressure sores in hospital it was 12·3 initially and 11·1 at the time the sore developed. Those patients without pressure sores had an average score of 15·4.

Our preliminary observations indicate the fundamental

1. Wilson, F., Sedzimir, C. B. *Lancet*, 1959, ii, 947.

importance of the general condition of the patient in determining the likelihood of development of pressure sores. We believe that this study will also allow a comparison to be made of the effectiveness of different nursing procedures in groups of patients with a variety of diseases. While it is possible that many of the traditional procedures, such as the application of spirit and powder and the rubbing in of soap, have little to commend them, the evidence so far submitted in favour of silicone creams is not conclusive. At the moment the widespread use of these expensive creams as a prophylactic measure for all patients who are nursed in bed either at home or in hospital is in our opinion unjustified. Large trials conducted by local health authorities and by medical and nursing teams in hospital are urgently required.

Whittington Hospital, Highgate Wing, London, N.19. A. N. EXTON-SMITH
DOREEN NORTON.

DIAGNOSIS OF BRUCELLOSIS

SIR,—Your review (Jan. 30) of my book agrees with me that we know little about this disease. It was for that reason that I wrote the book on brucellosis in England. I have evidently failed in my task, for your conclusion is that " many physicians will be unconvinced by the diagnosis in at least half the patients." The only reason you give for this extraordinary statement is that a rise in the titre of agglutinins after an injection of brucellin can be demonstrated in some apparently normal subjects.

I took as my criteria of diagnosis those advised by Wilson and Miles in a standard textbook [1] of bacteriology and immunology. In not one of my cases was " therapeutic success " used as the diagnostic weapon you suggest. Every one was confirmed by either an initial agglutination titre of 1 in 80, or a positive skin test, or a fourfold rise in agglutination titre after the skin test if that was negative.

Aside from this backing by eminent authorities I feel that your argument is a weak one. You might as well say that because many apparently normal persons have a positive reaction to the Mantoux test you do not believe that they have ever been infected with the tubercle bacillus. " Apparently normal " people may have a positive serum reaction for syphilis, toxoplasmosis, or other disease. Are we therefore to abandon the use of these tests and to ignore their results? It is true that the clinical history is important in the diagnosis of brucellosis, and indeed it is often the crucial factor in deciding whether to treat or not. Wilson and Miles say: " The interpretation of the agglutination test is not always easy, and demands a knowledge of the clinical history and the occupation of the patient." They also give this criterion which is less stringent than mine: " A titre of 1 in 20 to 1 in 80, in the presence of clinically undulant fever, may likewise be considered as practically diagnostic of this disease."

You are also guilty of a misuse of words. You say that my conclusions are dogmatic. Dogmatic means based on a-priori assumptions which are incapable of proof. If you read the book again carefully you will see that all the conclusions were based on the work of other investigators or my own observations. They cannot therefore be called dogmatic. Everyone who has anything original or unusual to put forward must expect to be disbelieved. I know that the correct thing to do with an ill-informed review is to ignore it; but it is important for the sake of the patients to protest in this case. So long as this unfortunate attitude of disbelief is exhibited towards the manifestations of chronic brucellosis, so long will cases be missed and much suffering which could be prevented will continue.

Bath. HUGH WALLIS.

*** Of Dr. Wallis' 35 proven cases, we make it that 15 were diagnosed by agglutination tests, 2 by skin tests alone, and 18 by a fourfold rise in agglutination titres *after* the injection of brucellin.

We accept the evidence of the agglutination tests, with the proviso that no single test confirms a diagnosis beyond any possible doubt.

Of the skin test, Wilson and Miles (p. 1911) say:

" Generally speaking the reaction resembles the tuberculin reaction in denoting the occurrence of infection without giving any clear indication of its activity . . . ; it may then remain positive for months or years. Great discretion has to be exercised in interpreting the test. In some countries 20–30 per cent of the population may react positively to it. It may be of value in survey work, but its use in the diagnosis of chronic brucella infection in the complete absence of other supporting laboratory findings should generally be discouraged. It is well to remember that, particularly in persons who have been previously exposed to brucella infection the intradermal injection of the test antigen may be followed by the appearance of circulating antibodies."

The W.H.O. committee on brucellosis believe that the intradermal test should not stand alone as supporter of the diagnosis.

As to the significance of a fourfold rise in titre after injection of brucellin, we have seen no convincing evidence to justify Dr. Wallis' interpretation. Brucellin, like any other antigen, produces antibodies: the amount produced is—to judge by experience with such things as T.A.B.—very variable. If the patient has had a previous infection—i.e., has a positive brucellin reaction—the titre will rise even higher than it will in a virgin; and in the circumstances we feel that Dr. Wallis places too much reliance on this serological reaction in making a diagnosis. That was one reason why we described his conclusions as " dogmatic ".

Re-examining the 35 case-histories in Dr. Wallis' book, we would say that half are probably brucella infections, and of the rest, some may be psychosomatic ailments and some P.U.O.s—and there are many causes of pyrexia in children about which we know little or nothing. Dr. Wallis' view seems to be that once a child has had a brucella infection any future vague illness is the same thing.—ED. L.

HYPNOSIS AND UNREGISTERED PRACTITIONERS

Dr. A. A. MASON, secretary, British National Division, International Society for Clinical and Experimental Hypnosis, writes:

" I have been approached by Dr. Ainslie Meares, the Australian president of the society, and Dr. H. Grant-Whyte, a member of the South African Medical and Dental Council, both of whom are investigating the problem of lay hypnotists and the possible harmful effects which can be caused by the use of hypnosis by unqualified practitioners. Dr. Grant-Whyte has approached the Minister of Health in an attempt to get legislation in South Africa along the lines of the British Hypnotism Act, 1952, and also in an attempt to restrict the practice of unregistered and untrained persons. It would be of great assistance to both these doctors to have available all the details of harmful effects which have followed the use of hypnosis by unregistered practitioners, and indeed if sufficient evidence is present it could stimulate similar action in this country. I should be grateful, therefore, if any doctors who have evidence from their own practice of patients suffering harm following the use of hypnotism by unqualified practitioners could communicate the details of such cases to me at 24, Avenue Road, Regent's Park, London, N.W.8. Of course, I need hardly assure the doctors and their patients that this matter will be treated in the strictest confidence."

1. Wilson, G. S., Miles, A. A. Topley and Wilson's Principles of Bacteriology and Immunology. London, 1955.

Parliament

Handicapped Refugees

IN the House of Lords on Feb. 2 Baroness ELLIOT OF HARWOOD asked if we could not mark World Refugee Year by admitting further immigrants into this country. The appeal for money was being very successful and the target of £2 million would be exceeded. About £125,000 had been already allocated for rehousing outside the camps in Austria, Germany, and Italy large families and old and infirm people, both groups which were difficult to move to other countries. £5000 was to be used for medical advice and to make a survey of people who had been many years in camp and whom it was difficult to take straight out and put into the world.

But the greatest stumbling-block to clearing the camps was the difficulty of resettling the handicapped refugees. They were brought before tribunals and turned down because of illness or suspected tuberculosis and they and their families had to remain in camp. In November the Government had given permission to bring in 210 handicapped refugees and their families. But there was still a great need for us to be more generous about handicapped refugees. The most recent figures showed that the number of handicapped refugees in camps is 10,000, comprising families of which one member is handicapped, and the number outside camps is 17,850. Of course, only a small proportion of handicapped refugees would want to come here. Some of them wanted to be settled in the area in which they had been working or had been educated, and many wanted to go to the New World to get away from European problems. But we could still take more here, and she asked the Government to consider altering slightly some of the terms under which people were brought here, and to be a little more generous, possibly, in statutory help for families should they by any chance fall again into difficulty after some years or not be in full employment.

Lord SHACKLETON pled for a more liberal application of some of the regulations. He thought that experience was beginning to show that some health regulations were completely pettifogging—for example, the unwillingness to admit people who had had tuberculosis, who had been cured, and were now living useful lives. He thought that we were putting unnecessary obstacles in the way, and in the process we and other countries had created great unhappiness.

Lord AMULREE agreed that it was a terrible thing if one member of a family which was acceptable here was found to have tuberculosis. Until quite lately that was an absolute bar to their admission. We all knew that in this country tuberculosis, particularly of the chest and lungs, was, to a large extent, a curable disease. Why were we so frightened of admitting people with this disease when there were facilities for treatment and good prospects of cure? He thought it improper that the Government would accept financial responsibility at no time for these unfortunate people. One could see that for the first few years they were here they should be supported by voluntary bodies, but it was expected that most of them would obtain jobs and settle down to become perfectly good, reputable, and productive citizens of this country. Why voluntary bodies who had money should be forced to keep sums aside in case these people fell on evil days in ten, twenty, thirty, or forty years' time he did not understand; and he trusted the Government would see their way to making these people eligible, when they came here as refugees, for the ordinary kind of benefits that a person living in this country would expect to obtain. The sum could not be large, but it was a very big sum for the voluntary organisations to have to put aside and tie up.

Baroness SWANBOROUGH said that the family unit was always of paramount importance. When a family was not only a family, but was the only asset that a small set of people possessed, it assumed very special proportions indeed. She felt that we should do our utmost to preserve the family in its entirety. The handicapped refugee families had been faced with years and years of misery in order not to break up their own unit. Because of a brother with tuberculosis, or a mother with cancer, or a small child who, through a brain injury, could never be a normal child, a whole family had lived all these years in a dreadful and unhappy way.

Government regulations, framed meticulously by men and women of good will but of chairbound experience, had forbidden the entry into various countries of people with disabilities, specified diseases, and handicaps. The debate had still ignored the fact that we were being allowed to bring into the country only people with handicaps that could be cured. She hoped that the Government would permit the entry within each family of a diseased or an incurable person who, despite the fact that he or she could not recover, could be looked after by his own family.

The Marquess of LANSDOWNE said that he had listened to the debate with sympathy but he felt that we should remember that a quarter of a million people had been received into this country, and that 1 in every 200 of the people of the United Kingdom at the present time had been refugees. 21 tuberculosis refugees had lately been admitted to the country, but it was correct that so far the regulations allowed only for curable cases. He believed that that attitude might be very sympathetically considered by the Department concerned. Wherever it was economically possible, the Government would continue to do everything in their power to unite families. Where there was a refugee settled in this country and earning money, members of the family were already allowed to come in. He believed that both the Home Office and the Ministry of Health tried to view this problem in a sympathetic way. A further survey of handicapped refugees was shortly to be made. He believed the opening of the gates to the handicapped refugee was an important achievement.

Public Health Laboratory Service Bill

IN introducing this Bill on Feb. 4, Viscount HAILSHAM explained that the P.H.L.S. had been started shortly before the late war by the Medical Research Council at the request of the Committee of Imperial Defence. Its original object was to provide a defence against possible enemy use of bacteriological warfare and against outbreaks of epidemic diseases. In the event, the service was not used to deal with any major emergency of this kind. On the other hand it came to be used by medical officers of health as a valuable aid to their ordinary work. Only in the areas of some of the larger local authorities had any such service previously been available. Indeed, the main reason for creating the service had been the inadequacy of the arrangements before the war for public-health bacteriological work. Thus, it came about that a service which had been designed for an emergency became an indispensable part of normal peace-time administration. It was therefore decided after the war to maintain it as part of the regular machinery for the diagnosis and control of infectious diseases. The M.R.C. had continued to administer it as agents for the Minister of Health.

The P.H.L.S. at present consisted of a central laboratory, 8 regional laboratories, and 51 area laboratories. There were several special reference libraries, some at the central laboratory and some in other institutions. The service was considered now to be fully developed, and no increase in the number of laboratories was planned. The staff numbered 1068, of whom 126 were medically qualified. The annual cost of the service was about £1,262,000.

The M.R.C. had for some time been anxious to divest themselves of responsibility for the service, and to substitute a permanent organisation responsible to the appropriate executive department for what was always an anomalous and temporary arrangement. The work of the P.H.L.S. was really peripheral to the M.R.C.'s interests, for they were mainly concerned with research, while the service, though scientific, was largely routine and research was included only as a secondary function. There was some inconvenience in the anomaly that the M.R.C. were responsible for their normal activities to the relevant Privy Council committee, and for the P.H.L.S. to the Minister of Health. The position was also somewhat embarrassing for the M.R.C. as employers of labour. The level of remuneration of their own staff was related to that of the staffs of universities. The remuneration of the P.H.L.S. staff was related to that of staffs of hospitals in the National Health Service.

The executive work of the P.H.L.S. had remained with the M.R.C.'s headquarters staff, but the ordinary work of the Council and of their headquarters staff had continued to grow, so that it had now become necessary for the P.H.L.S. to be given its own administrative machinery as soon as possible so as to release the headquarters staff of the M.R.C. Accordingly, it was decided to introduce this Bill which would enable the Minister of Health to administer the service through a new Public Health Laboratory Service Board which he would appoint.

The board would be a separate entity, with legal status, and it would employ staff and hold property in its own name. It would be analogous to a regional hospital board—that is to say, it would administer the service as the agent of the Minister. It would be appointed by the Minister and its staff would not be Civil Servants. It would be subject to the directions of the Minister, whose control of the service would thus remain more or less as at present.

The board would consist of a chairman and one other member, both medically qualified, two members appointed after consultation with the M.R.C., two members with experience as bacteriologists, two members who were medical officers of health of local authorities, and two members with administrative experience.

Lord TAYLOR described the P.H.L.S. as a kind of national medical Scotland Yard. It differed only in that it had its peripheral units scattered all round the country and did not have to wait for a county police force to call it in. It did, however, have to be called in by somebody, and the people who called it in were medical officers of health, hospitals, or local doctors. One great feature of the service was that staff had always been available for personal consultation. They had come out to see cases, investigate problems on the spot, and help doctors with any kind of epidemiological problem.

The P.H.L.S. had also done an immense amount of research, and he was a little sorry to hear Viscount Hailsham say that the bulk of its work was routine and that it was not primarily a research organisation. Lord Taylor hoped that this transfer of functions would not entail any lessening of the research activities of the service. The service had put Britain in the forefront of bacteriology and epidemiology. The World Health Organisation had recognised the central laboratories of the service at Colindale as the World Influenza Centre. It had also a virus reference library, a mycological reference library and an air hygiene unit. It had an epidemiological research unit at Cirencester run by a part-time general practitioner. On the purely bacteriological side the service maintained centres which concerned the whole of Europe and the Commonwealth for serological typing, particularly of salmonella and dysentery organisms. Research ranged from bacteriological structure and metabolism to such practical questions as the design of operating-theatres and the bacteriology of public telephones and iced lollipops.

Viscount Hailsham had also mentioned that the service was primarily linked with the medical officers of health. Lord Taylor believed that it was also linked, perhaps more closely than was generally realised, with the hospital services. In some places the public-health laboratory functioned as a general-hospital bacteriological laboratory, doing the routine bacteriology for that hospital and for the general practitioners as well as its own specialised work on milk, water, shell-fish, and ice-cream. In other places it did specialised work only. It had been suggested that the right thing would be to make the P.H.L.S. part of the regional hospital board service. But Lord Taylor was sure that the decision taken by the Government was the right one. The service should be kept as an entity, for bacteria knew no regional boundaries. Moreover, there must be a central reference organisation, if these germs and viruses were to be identified in the increasingly difficult varieties in which they occurred.

Turning to the membership proposed for the new board, Lord Taylor said that he could see no reason for the stipulation that the chairman should be medical. It was widely believed in the P.H.L.S. that the intended chairman might be the chief medical officer of the Ministry of Health. Lord Taylor thought this a bad idea, because the chief medical officer was an exceedingly busy person and because the board should have an autonomy, a vigour, and a life of its own. It should be the servant of the Minister and subject to his general direction, but it should bat on its own wicket and not be tied to the Ministry. The job of chairman called for someone who would give a good deal of time to it. 40 or 50 laboratories were scattered about the country. If the chairman went round and saw every laboratory once a year it would be for the good of the staff. Lord Taylor regretted that there was no representative of the hospitals, though the service was closely linked with the hospitals, or of the general practitioners, though the general practitioners were exceedingly interested in the kind of research which the service did. He was also disappointed that there was no representative of the staff on the board.

Lord AMULREE suggested that, as the board would work closely with the regional hospital boards, it might not be a bad idea to have on the board one of the senior medical officers who advised the hospital boards. He, too, hoped that there would be some representation of the hospital service and general practice. Another important point was that there should be one lay member.

Viscount HAILSHAM agreed that to keep a service alive it was necessary to include research in its activities, and the P.H.L.S.'s research activities were important and creditable. It was mainly for that reason that it was proposed that two members of the board should be appointed after consultation with the M.R.C. The composition of the board would probably be considered on the committee stage of the Bill. Though the schedule did not contain a direct reference to a hospital representative, a number of medically qualified people would have to be appointed to the board, including bacteriologists and others, and he would have expected to find that the board contained names which came from the hospital service.

Powers of Subpœna

ON Feb. 2 at the end of the committee stage of the Professions Supplementary to Medicine Bill a Government amendment was carried to remove the power of subpœna from the disciplinary committees to be set up under the Bill. Miss EDITH PITT, parliamentary secretary to the Ministry of Health, explained that the Government thought that the subpœna provisions should be omitted until the Simonds Committee had reported. The matter could then be reconsidered. The Bill would still enable the disciplinary committees to administer oaths. It was hoped that the Simonds report would be ready before the Bill left the floor of the House.

QUESTION TIME

General Practitioners' Central Fund

Mr. BARNETT JANNER asked the Minister of Health how much Exchequer contribution had been deducted annually from the General Practitioners' Central Fund since 1955, how it was computed, and what was the relationship between the Exchequer contribution annually deducted from the Fund and the employers' contribution to the National Health Service compulsory superannuation scheme; and how he proposed to increase the employers' contribution so as not to reduce the sum to be distributed to general practitioners. Mr. WALKER-SMITH replied: The amount of the Exchequer superannuation contribution deducted from the Central Pool is the aggregate of the employers' superannuation contributions paid by the executive councils for the general medical practitioners with whom they are in contract. The amounts involved were, for Great Britain:

	£
1955–56	3,529,607
1956–57	3,569,494
1957–58	3,809,181

The superannuation position of practitioners cannot be considered further until the Report of the Royal Commission on Doctors' and Dentists' Remuneration has been received and considered. I have, however, given an assurance that the supplementary employer's contribution which is being intro-

duced to help liquidate the deficiency in the health service superannuation scheme will not have the effect of reducing the current net remuneration of general practitioners. The detailed method of achieving this has still to be discussed with the profession.

Mr. JANNER: In considering this matter, will the Minister take into account the fact that the proportion which is being deducted, which is 8%, was given as 2% less by the actuary in 1955? In view of that, will he refund to the general practitioners the loss they have incurred thereby? Mr. WALKER-SMITH: I do not think that that point arises. The general situation which the hon. Gentleman wishes to safeguard is really dealt with in the penultimate sentence of my answer.

Lay Hospital Staff

Dr. A. D. D. BROUGHTON asked the Minister the number of personnel, other than medical and nursing staff, employed in hospitals in England and Wales when the National Health Service came into operation in July, 1948, and the number at the latest convenient date. Mr. WALKER-SMITH replied: In round figures 197,000 at the end of 1948 and 250,000 at the end of 1958. This includes professional, technical, works, maintenance, domestic, administrative, and clerical staff.

Preludin (Phenmetrazine)

Mr. MARCUS LIPTON asked the Home Secretary whether he had now received the report of the Poisons Board on 'Preludin'; and whether he would now ban the sale of this drug without medical prescription.—Mr. R. A. BUTLER replied: I have now received from the Poisons Board a report concerning a recommendation that a number of substances including preludin should be supplied only on prescription. Subject to the consideration of any representations by those concerned, I propose to accept this recommendation and to give it effect as soon as practicable.

World Refugee Year

Mr. D. E. C. PRICE asked the Home Secretary whether, in pursuance of the support of the World Refugee Year, he would admit another 1000 refugees to this country before Easter—Mr. R. A. BUTLER replied: Arrangements are being made in consultation with the United Kingdom Committee of the World Refugee Year, to ascertain the number of specially handicapped refugees who wish to come to this country and can be adequately sponsored by the voluntary organisations. I shall consider the matter further when this information is available.

Medicine and the Law

A Difficult Patient

SECTION 172 of the Public Health Act, 1936, dealing with precautions against exposure of the public to infectious diseases, sets out the conditions under which action may be taken to restrain infectious persons who refuse to accept precautionary measures. This section of the Act was reluctantly invoked in Oxford last week to send to hospital for three months a woman of 52 who was known to have had pulmonary tuberculosis for twelve years.

In April, 1948, after a hæmoptysis, she was found to have pulmonary tuberculosis with a probable cavity, but she refused to attend the chest clinic. She was offered a bed in hospital at any time convenient to herself but again refused. In July, 1948, she was found to be pregnant. Home conditions were very bad, and 4 adults and 2 children were occupying one room in a basement, so the family was ultimately rehoused in August, 1949. During this time repeated requests to attend the chest clinic were ignored. On one occasion she promised to attend if transport was provided, but an ambulance called three times without success. Nothing further could be done, and the family was removed from the chest-clinic register.

In August, 1951, another attempt was made to get her to the clinic, but it failed. Finally in March, 1954, she became very ill and she was admitted to hospital as an emergency. Her sputum was loaded with tubercle bacilli and she had gross bilateral tuberculosis. She remained in hospital having chemotherapy for three months, and then discharged herself against advice. She still had extensive and very unstable cavitated disease with a positive sputum, but there had been definite improvement. One of her children had phlyctenular conjunctivitis and was under care for several years. Her other child also had primary tuberculosis, for which his mother refused hospital treatment.

After her discharge, there was a period of intermittent observation at the clinic and evidence of some improvement in her tuberculosis. In September, 1954, she described symptoms which may have been due to drug intolerance, and streptomycin was withdrawn, although she was supposed to continue on P.A.S. and isoniazid. In December, 1956, laryngeal-swab culture was positive for tubercle bacilli. Further attempts, both by the clinic staff and by the medical officer of health, to get her to attend during 1957 were unsuccessful. At the end of 1958 it was thought that she was working in a canteen. In January, 1959, she was brought to the clinic by the chief public-health inspector in his car. Bronchial lavage gave a positive culture for tubercle bacilli, which showed normal sensitivity to anti-tuberculous drugs. X-ray examination showed extensive fibrotic disease which had not spread since November, 1956. She maintained that she had had chemotherapy ever since she last attended the clinic, but this was not confirmed by the doctor she named. Last December bronchial lavage was again positive and radiologically the disease had extended.

It was clear that she was infectious to other persons, that she would accept treatment only under duress, and that her promises to carry out treatment at home were quite unreliable. On Feb. 4 the Oxford magistrates granted an order to Oxford City Council that she should be taken to the Osler Hospital for three months.

We are indebted to Dr. F. Rjdehalgh for supplying this information.

Obituary

EILEEN MARY HICKEY

M.D., B.Sc. Belf., F.R.C.P.I., D.P.H.

Dr. Eileen Hickey, who died on Feb. 3 at her home in Belfast at the age of 75, was distinguished both as a physician and as a member of the Parliament of Northern Ireland.

In her early life she entered the Civil Service, and it was not until she was in her early thirties that she decided to qualify in medicine. She returned to Belfast and studied at Queen's University. Her student career was marked by enthusiasm and by impatience to be qualified; and also by a positive enjoyment of the written examination which amazed her more usually pen-tied contemporaries. She graduated M.B. with first-class honours in 1921 and two years later obtained the M.D. with a gold medal. Her career as a physician was based on the Mater Infirmorum Hospital in Belfast, and she became senior physician and a member of the board of governors. She examined in medicine at the university, was for many years a member of the senate, and was the first woman to be elected president of Queen's Graduates Association.

A. H. B. writes:

"Eileen Hickey had a ready pen and spoke fluently and entertainingly. It was no surprise to her fellow graduates when she was returned in 1949 as one of the four members representing the university in the Northern Ireland Parliament. She was returned as an Independent in a Parliament where politico-religious feeling ran high. She was again returned in 1953, but owing to failing health did not seek re-election in 1958.

"She had many outstanding qualities. Among them were a great sense of responsibility in everything she undertook and a deep sympathy for old people. Her indignation was easily aroused on behalf of any person or cause that she thought

unfairly treated. She was a bonny fighter and a most staunch friend. She worked hard for the cause of old people's homes when she was a member of the Council of Social Service in Northern Ireland, and, after the late war, she organised the sending of parcels to refugees and others impoverished by their war-time experiences. She had a great love of gardening and of flowers.

"She faced with fortitude her years of declining health and did not allow herself the indulgence of self-pity. Her Church was very real to her and was a support and an abiding interest. She will be remembered by her university as a great character, and by her friends for her lively wit, dauntless spirit, and many acts of great kindness."

RAYMOND EBENEZER APPERLY
M.R.C.S., F.F.A. R.C.S., D.A.

Mr. Raymond Apperly, consulting anæsthetist to the Middlesex Hospital, London, died on Jan. 29 at Evesham, at the age of 76.

He was born in Stroud, Gloucestershire. His father, Mr. Ebenezer Apperly, L.D.S., had been a dental student at the Middlesex Hospital, and in due course Raymond, following what was becoming a family tradition, joined the medical school. He qualified in 1907, and after holding house-posts at the Middlesex he was appointed anæsthetist to the Hospital for Sick Children, Great Ormond Street. In 1910 he joined the anæsthetic department at the Middlesex Hospital and later became lecturer in anæsthetics at the medical school. In 1931 he succeeded Dr. Herbert Charles as senior anæsthetist. He took the D.A. in 1935 and was elected F.F.A. R.C.S. in 1948.

H. P. C., who was a student with Apperly nearly sixty years ago, writes:

"Raymond Apperly was a cheerful, friendly soul, popular alike with men, women, and children. He had an extensive private practice, as I discovered if he was ill. To give an anæsthetic to a patient who had already been sent to sleep by Apperly was not easy, for their disappointment was often so evident. One Saturday, years ago, the school doctor in Sussex phoned that my son had an acute appendix which should come out that day when he arrived by ambulance. At 5 P.M. Apperly appeared with the surgeon. Some time later I found out that he was spending the day at Lancing with his son but had cut it short to help a friend. Such was the man. A delightful colleague who will be remembered with affection by the old brigade."

Mr. Apperly leaves a widow, a daughter, and a son who is in practice at Evesham.

ALEXANDER HUGH DICKSON SMITH
M.C., T.D., M.B. Edin., D.L.

Dr. Smith, who died on Jan. 31 at the age of 69, spent many years in practice in his native Llanelly and played a large part in the settlement of the "Llanelly dispute" of the mid '30s.

He was educated at Llandovery College and the University of Edinburgh, where he qualified in 1914. The same year he joined the R.A.M.C. and went to France, where he became attached to the Guards Division. He was awarded the M.C. for conspicuous bravery in 1917. He served later with the 3rd and 29th Divisions and finished his war service in India. On his return to Llanelly he at once entered general practice. Soon afterwards he joined the staff of Llanelly and District Hospital. He did most of the surgical work there and became the first honorary radiologist to the hospital.

As a member of the Territorial Association he was sent on the outbreak of the late war to France with the rank of lieut.-colonel. He returned from France in 1940 and thereafter acted as O.C. to units in Western Command. At this time he gave up his general practice, but he remained extremely active in medical affairs in South Wales: he was chairman of many committees, including the Ministry of Pensions boards for Swansea and Carmarthenshire, the committee under the Disabled Persons Act, and the Carmarthenshire panel, insurance, and executive committees. He was high sheriff of the County of Carmarthen for 1944 and 1945, and deputy lieutenant in 1952.

He married Joan Margaret, daughter of the late Dr. Hugh John. She survives him, with their daughter.

Diary of the Week

FEB. 14 TO 20

Monday, 15th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Diagnosis of Organic Confusional States.
GUY'S HOSPITAL, S.E.1
5.30 P.M. Prof. Douglas Hubble: Virilism.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Prof. R. B. Hunter: Virilising Syndromes—Problems of Intersex.

Tuesday, 16th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Prof. Arnold Sorsby: Optical Components During the Growth of the Eye.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. C. H. Gray: Non-pancreatic Aspects of Diabetes Mellitus.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. Jack Suchet: Appraisal of the Results of Treatment of Infertility.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. A. D. Gordon: Ultrasonic Rays in Neurosurgery.
OSLER CLUB OF LONDON
8 P.M. (Wellcome Building, Euston Road, N.W.1.) Dr. Kenneth Dewhurst, Prof. G. E. Trease: Thomas Dover (born 1660).
LEEDS NEUROLOGICAL SCIENCIES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. J. W. D. Bull: Radiological Investigation of Strokes.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. Adam Patrick: Symptoms of Diabetic Coma: a Retrospect.

Wednesday, 17th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.15 P.M. *General Practice.* Dr. R. A. P. Paul, Mr. H. G. Hanley, Dr. R. L. Bodman: Prostatectomy—Early or Late?
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Pigmented Lesions of the Skin.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. J. R. Belcher: Surgical Treatment of Lung Cancer.
EUGENICS SOCIETY
5 P.M. (Manson House, Portland Place, W.1.) Dr. Eliot Slater: Galton's Heritage. (Galton lecture.)
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Queen's College, Dundee.) Dr. J. M. Stowers: Investigation of Hypoglycæmic Agents.

Thursday, 18th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. M. O. Skelton: Pathological Conditions of the Pulmonary Tissues. (Erasmus Wilson demonstration.)
UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Dr. Harris Isbell (Bethesda): Pharmacology of Opiate Addiction.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. E. M. Vaughan Williams: Relations Between Contractions and Intracellulary Recorded Potentials in Cardiac Muscle.
ROYAL SOCIETY OF MEDICINE
4.45 P.M. *Dermatology.* Dr. W. Frain-Bell: Grenz Rays in the Treatment of Benign Dermatoses.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, Manson House, 26, Portland Place, W.1
7.30 P.M. Dr. T. F. Davey: Recent Chemotherapeutic Work in Leprosy.
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. Sydney Blackman: Rotational Tomography of the Face.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Dr. Alick Isaacs: Prospects for a Viral Antibiotic.
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P.M. Mr. Denis Browne: Orthopædics of the Fœtus.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Dr. C. Kerr McNeil: Orthopædic Principles in the Treatment of Lip and Palate Clefts.

Friday, 19th

UNIVERSITY OF LONDON
4.45 P.M. (St. Bartholomew's Hospital, E.C.1.) Prof. J. Loewenthal (Sydney): Contributions to Surgical Research.
ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Dr. J. D. Cottrell: The Role of the World Health Organisation in Epidemiology.
8.15 P.M. *Radiology.* Mr. P. T. Savage, Mr. S. L. Strange, Dr. Gordon Osborne, Mr. N. R. Barrett, Dr. Brian Creamer, Dr. J. W. Pierse: Dysphagia.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Prof. A. S. Johnstone: Hiatus Hernia.
4 P.M. Dr. Fraser Roberts: Medical Genetics.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. W. D. Doey: Foreign Bodies in the Ear, Nose, and Throat.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.20 P.M. Dr. Macdonald Critchley: History of our Conception as to the Origin of Language in Man. (Part I).
PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields) Discussion: Medicine and the Law.

Notes and News

WORLD HEALTH ORGANISATION

THE executive board ended its session on Feb. 1. The proposals of the director-general, Dr. M. G. Candau, for W.H.O.'s 1961 programme and regular budget of $18,569,620, were unanimously recommended to the Health Assembly which opens in Geneva on May 3. The board approved steps taken towards the building of a new headquarters for the Organisation in Geneva. On a site not far from the Palais des Nations, this will cost about 40 million Swiss francs, of which 20 million is to come from the Swiss Federal authorities in the form of an interest-free loan, and 10 million is to be made available by the Republic and Canton of Geneva, which is also giving the site. The architectural competition closes on April 14.

Only about 1 million dollars is now needed to finance W.H.O.'s share of the costs of malaria eradication for 1960, but $6·4 million is needed to ensure continuation of the work in 1961.

Figures released on Jan. 29 show that the world incidence of plague was as low last year as in 1958; fewer than 300 cases of human plague were officially reported in ten countries of Africa, America, and Asia (outside continental China). The occurrence of "accidental" single cases (in the United States of America and Madagascar) and of small foci in areas which had been apparently free from human cases for one or more years (in Northern India and in the Union of South Africa) indicates that the infection is maintained among rodents in wide areas of the three continents. Burma notified the highest number of cases (98).

Cholera incidence in 1959 was unusually low in India, and, in spite of the presence of the disease in Thailand and its considerable increase in East Pakistan during October and November, fewer than 42,000 cases were officially reported in Asia (excluding China), compared with about 95,000 in 1958 and 64,000 in 1957. "In India the situation was probably the most favourable on record. Less than 14,000 cases were provisionally notified against 67,000 reported in 1958."

SUPPLEMENTARY ESTIMATES

THE supplementary estimate for the National Health Service in the current financial year [1] shows an increase for England, Wales, and Scotland of £25,600,000, bringing the total net cost to £562 million. Of the additional sum £15 million goes to the revenue account of hospital boards, mainly to meet salary and wage increases; £6 million to the pharmaceutical services because of an increase in the number of prescriptions and higher average costs per prescription; and £1 1/3 million to meet the increased demand for poliomyelitis vaccine.

O & M

FIRST reaction to the latest report [2] by the Hospital Organization and Methods Service may be that it is all obvious and simple: so it is, but there is no doubt that it is also a necessary and sad commentary on some aspects of the National Health Service. The report concerns the activities of chest clinics, including the design of an outpatient appointments system, the efficient use of the time of staff and patients, and the keeping of medical records. Chest clinics are used merely as an illustration. They are well chosen for this purpose; for they are often relatively small self-contained units handling large numbers of "new" and "old" patients, and therefore easy and profitable to study. The fact that they are the subject of this report does not mean that they are either better or worse organised and run than any other branch of the N.H.S.

The instructions for studying the problem of efficient flow of patients in a clinic are clearly expressed and easy to carry out. It is almost a shock to see a whole-page diagram whose sole purpose is to illustrate that the rate of flow is determined by the speed of the slowest process. The same applies to the movements of armies and was discovered long ago. But if this and similar "rules" were widely acknowledged and acted on there would be no need for O & M surveys. The report concludes:

"The great bulk of matters dealt with here is concerned with efficiency of a fairly mechanical kind. It is recognised that this efficiency ranks only second in importance to the standard of medical and nursing care which is given to the patients. These two aspects are not, as is sometimes assumed, conflicting, but complementary. Medical care is hampered if case-notes go astray, and medical skill of the highest quality is wasted if the patients become disgruntled and do not come to take advantage of it. If, on the other hand, medical skill is practised in an environment of orderliness, if waste of time and effort are eliminated, and if the general, as distinct from the purely medical, well-being of the patients is secured, the maximum benefit will be derived from the services provided."

1. 1959-60: Supplementary Estimates and Estimates for Revenue Departments. H.M. Stationery Office. 1960. Pp. 171. 9s. 6d.
2. Chest Clinics. Hospital Organization and Methods Service Reports, no. 3. H.M. Stationery Office. 1959. 1s. 9d.

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names:

Approved name	*Other names*
Bamethan	2-*n*-Butylamino-1-*p*-hydroxyphenylethanol Vasculit is the sulphate
Bendrofluazide	3-Benzyl-3:4-dihydro-7-sulphamoyl-6-trifluoromethyl-benzo-1:2:4-thiadiazine 1:1-dioxide Aprinox
Carbolonium Bromide	Hexamethylenebis (carbamoylcholine bromide) Imbretil
Carisoprodol	2-Carbamoyloxymethyl-2-*N*-*iso*propylcarbamoyloxypentane
Cetylpyridinium Chloride	1-Hexadecylpyridinium chloride Ceepryn
Cyclandelate	3:3:5-Trimethyl*cyclo*hexyl mandelate Cyclospasmol
Cyclophosphamide	2-[Di-(2-chloroethyl)amino]-1-oxa-3-aza-2-phospha*cyclo*hexane 2-oxide Endoxan; Cytoxan
•Dextropropoxyphene	*a*-(+)-4-Dimethylamino-1:2-diphenyl-3-methyl-2-propionyloxybutane Darvon is the hydrochloride; Doloxene is the hydrochloride
Dimethoxanate	2-(2-Dimethylaminoethoxy) ethyl phenothiazine-10-carboxylate
Diphenadione	2-Diphenylacetylindane-1:3-dione Didandin; Dipaxin; Oragulant
Diphenoxylate	Ethyl 1-(3-cyano-3:3-diphenylpropyl)-4-phenyl-piperidine-4-carboxylate
Disulphamide	5-Chloro-2:4-disulphamoyltoluene Disamide
Heptabarbitone	5-Ethyl-5-*cyclo*hept-1′-enylbarbituric acid Medomin
Nialamide	*N*-(2-Benzylcarbamoylethyl)-N′-*iso*nicotinoylhydrazine Niamid
Phenazocine	2′-Hydroxy-5:9-dimethyl-2-phenethyl-6:7-benzomorphan
Phenprocoumon	4-Hydroxy-3-(1-phenylpropyl)coumarin Marcoumar
Salazosulphadimidine	4′-(4:6-Dimethylpyrimid-2-ylsulphamoyl)-4-hydroxy-azobenzene-3-carboxylic acid Azudimidine
Sulphaphenazole	5-*p*-Aminobenzenesulphonamido-1-phenylpyrazole Orisulf
Tetrahydrozoline	2-(1:2:3:4-Tetrahydro-1-naphthyl)imidazoline Tyzanol is the hydrochloride
Trimustine	Tri-(2-chloroethyl)amine Trillekamin

• Replaces the approved name propoxyphene for α-(+)-4-Dimethylamino-1:2-diphenyl-3-methyl-2-propionyloxybutane.

Proprietary name	*Approved name reference*
Aprinox	Bendrofluazide
Azudimidine	Salazosulphadimidine
Ceepryn	Cetylpyridinium Chloride
Cyclospasmol	Cyclandelate
Cytoxan	Cyclophosphamide
Darvon	Dextropropoxyphene
Didandin	Diphenadione
Dipaxin	Diphenadione
Disamide	Disulphamide
Doloxene	Dextropropoxyphene
Endoxan	Cyclophosphamide
Imbretil	Carbolonium Bromide
Marcoumar	Phenprocoumon
Medomin	Heptabarbitone
Niamid	Nialamide
Oragulant	Diphenadione
Orisulf	Sulphaphenazole
Trillekamin	Trimustine
Tyzanol	Tetrahydrozoline
Vasculit	Bamethan

Association of Industrial Medical Officers

This Association is offering in 1961 a prize (50 guineas) for an essay from a member on research on occupational health. Further details may be had from the hon. secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

University of Oxford

Sir Lindor Brown, Jodrell professor of physiology at University College, London, has been appointed Waynflete professor of physiology in succession to Prof. E. G. T. Liddell, who is retiring under the age-limit.

Sir Lindor, who is 56 years of age, was educated at the Boteler Grammar School, Warrington, and the University of Manchester, where in 1924 he took his B.SC. with honours in physiology and was awarded a Platt physiological scholarship. The following year he took his M.SC. In 1928 he graduated M.B., and in the same year he was appointed lecturer in physiology at the University of Leeds. He worked there on gastric innervation with the late B. A. McSwiney and on transmission through sympathetic ganglia. In 1934 he joined the scientific staff of the Medical Research Council, working in Sir Henry Dale's laboratory on transmission at nerve-endings by acetylcholine. In the early years of the war he worked on military problems, spending some time in the laboratory at Lulworth. In 1942, when the Royal Naval Personnel Research Committee was set up, he became its secretary, and until 1945 he was directing work in his own laboratory on underwater physiology, dealing particularly with problems affecting submarine crews and divers using self-contained gear. He was appointed to the Jodrell chair in 1949. He was a member of the Medical Research Council from 1951 to 1955 and of the Advisory Council on Scientific Policy from 1956 to 1959. He has been successively secretary of the Physiological Society, an editor of its journal, and foreign secretary. He was elected F.R.S. in 1946, and became biological secretary of the Royal Society in 1955 and a vice-president in 1956. He was elected F.R.C.P. in 1958. In 1947 he was appointed C.B.E., and in 1957 he was knighted.

University of Cambridge

On Jan. 23 the following degrees were conferred:

M.B., B.Chir.—A. J. H. Nix.
M.B.—*J. D. Allison, *John Farmer, D. H. Keeling, C. J. F. L. Williamson.

* By proxy.

University of London

Dr. H. O. Schild, reader in pharmacology at University College, has been appointed to the chair of pharmacology at the college.

Dr. Schild took the degree M.D. Breslau in 1932 and joined the scientific staff of the Medical Research Council at the National Institute for Medical Research in London. He has worked in the departments of physiology and pharmacology of Edinburgh University, and in 1937 he joined the staff of the department of pharmacology at University College, London. In 1935 he took the PH.D. Edin. and in 1950 the D.SC. Lond. His published work includes studies on the principles of biological assay, drug antagonism, and an extensive series of papers on the mechanism of the anaphylactic reaction and histamine. He is joint editor of the 1959 edition of *Applied Pharmacology*.

Dr. W. F. Widdas, reader in physiology at King's College, has been appointed to the chair of physiology at Bedford College.

Dr. Widdas qualified M.B. from the University of Durham in 1938 and has since taken the degrees of PH.D. and D.SC. of the University of London. He held a senior lectureship in physiology at St. Mary's Hospital Medical School before taking up his present post. During the late war he served with the R.A.M.C. with the rank of major.

Dr. Hermann Lehmann, senior lecturer in chemical pathology at St. Bartholomew's Hospital Medical College, has been appointed to the readership in that subject at the college.

The title of reader in chemical pathology has been conferred on Dr. G. R. Webster in respect of his post at Guy's Hospital Medical School.

Royal College of Physicians of Ireland

At a meeting of the college on Feb. 5, with Dr. P. T. O'Farrell, the president, in the chair, the following were admitted to the licence and membership:

Robert Carroll, D. C. Curtin, J. P. Duffy, J. S. Wright.

Royal Australian College of Physicians

The following officers of the college have been elected for 1960–62:

President, T. M. Greenaway (Sydney); vice-presidents, F. R. Hone (Adelaide), H. M. Rennie (Sydney), E. H. Roche (Auckland); censor-in-chief, K. B. Noad (Sydney); hon. treasurer, G. B. D. Hall (Sydney); hon. secretary, R. L. Harris (Sydney).

Royal College of Physicians of Edinburgh

At a meeting on Feb. 2, with Dr. A. Rae Gilchrist, the president, in the chair, the following were elected to the membership:

A. L. K. Rankin, Raghunath Singh Hoon, I. S. Trotter, Bomullage Dilipkumara Dharmasena, Mohd. Hayat Zafar, K. D. Coorey, Mary Cherian, R. S. Wells, S. J. Surtees, G. P. Lewis, D. J. Woods, W. A. G. Roper, Ramji Singh, Sushil Kumar Mitra, Bhattarahalli Gururao Srinivash Murthy, Colin Protheroe, J. C. Maclaurin, Prasanta Kumar Basu, Kandathil Mammen Cherian, Tin Ohn, Nabiha Hasan Rizavi, Krishna Kant Sinha, Roop Kishore Seth, Ma Hnin Yee, Kathleen A. Irvine, G. W. Fenton, Francis Moran, Narayanarao Ambajeerao Jadhav, Freda M. Paul, Ishaa Sh'Aibu Audu, Chinganezhath Krishnan Ramachandran, Yip Chong Wong, J. S. Fleming, Vetherednam Thuraisingham, F. P. Retief, J. G. Richards, Manasija Sarkar, L. L. Wilson, Kottaram Venkatachala Sarma Krishna Das, Upamaka Brahmaji Rao, F. Po-Tun Fok, W. E. Ince, I. T. Draper, Sydney Louis, E. S. Paykel, Anupam Das Gupta, D. F. Scott.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the Faculty on Feb. 1 with Mr. Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship:

Perinkulam Krishnaswami Ramaswami qua physician; Ratan Lal Agarwal, Alumootil David George qua surgeon.

Lady Tata Memorial Trust

The trustees of this fund invite applications for grants, scholarships, and fellowships for research on blood diseases, with special reference to leukæmia.

Programmes of research on any aspect of malignant disease which may throw light on problems of leukæmia will be considered and awards may be made to investigators of any nationality, working in any country where payment can be made. Application forms may be had from the secretary of the (European) Scientific Advisory Committee of the Trust, Chester Beatty Research Institute, Fulham Road, London, S.W.3. Applications must be submitted before March 31.

Scottish Health Services Council

Mr. John Dunlop has been appointed chairman of the council in succession to Prof. G. L. Montgomery.

International Congress on Alcohol and Alcoholism

This congress will be held from July 31 to August 5, in Stockholm. Further particulars may be had from the congress secretary, Box 5071, Stockholm, 5, Sweden.

Universities Federation for Animal Welfare

The annual general meeting of this Federation will be held on Tuesday, Feb. 16, at 6 P.M., at the Conway Hall, Red Lion Square, London, W.C.1, when Major C. W. Hume will report on his recent visit to the conference of the Animal Care Panel in America. At 8 P.M. there will be a brains trust.

Surgeon Captain F. P. Ellis, of the Medical Department of the Admiralty, has been awarded £100 and a medal by the Chadwick Trust in recognition of his work during the last five years in promoting the health of Royal Navy personnel.

Courses for candidates for the D.M.R.D. and D.M.R.T., starting in October, are now being organised by the Faculty of Radiologists. Further particulars may be found in our advertisement columns.

The British Council for Rehabilitation and the University of St. Andrews will hold a conference from March 29 to 31, at Queen's College, Dundee. The subject will be rehabilitation—its industrial and social implications. Further particulars may be had from the general secretary of the Council, Tavistock House South, London, W.C.1.

The North of England Otolaryngological Society will hold a meeting in Hull on Saturday, Feb. 20, at 2 P.M.

Appointments

BRITAIN, ELIZABETH, M.B. Lond.: assistant M.O., Brigg and Barton area of Lindsey.
MCNEIL, N. L., M.B. Lond., D.O.M.S.: consultant ophthalmologist, Barnsley group of hospitals.
MARSHALL, BARBARA S. M., M.B. Birm.: assistant M.O., Worcestershire.
NICHOLSON, BASIL, M.B. Manc., D.P.H., D.T.M. & H.: assistant M.O.H. and school M.O., Gloucestershire.
OCCLESHAW, J. V., M.B., B.SC. Lpool, D.M.R.D.: consultant radiologist, regional neurosurgical centre, Walton Hospital, Liverpool.
OWEN, GORONWY, M.B. Wales: consultant pathologist, Doncaster group of hospitals.
WRIGHT, J. T., D.M. Oxon., M.R.C.P.: part-time consultant physician, St. John's Hospital for Diseases of the Skin, London.